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Research Article

Predicting COVID-19 Cases and Deaths Utilizing Hygiene Hypothesis Surrogate Factors: A Global Analysis

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Abstract

At the beginning of the pandemic, it was difficult to determine which factor or set of factors could be analyzed to determine where coronavirus disease 2019 (COVID-19) cases and deaths could be expected to surge globally. This study, utilizing surrogate factors representing the hygiene hypothesis, sought to examine if correlations between the various factors existed.

Data publicly available from 190 countries were collected. These data included COVID-19 total case numbers and deaths through December 28, 2020; water, sanitation, and hygiene (WaSH) metrics; data on mortality due to various types of air pollution; and additional factors such as control of solid waste, emission growth rate of methane and carbon dioxide, and daily adjusted life years lost to unsafe drinking water and sanitation. These elements were analyzed using multiple regression analyses to determine the combination of factors most predictive of COVID-19 total cases and deaths via IBM SPSS 27.0. Separate regressions were conducted for the two criterion variables.

The analyses revealed positive correlations between two predictor variables: a nation's mortality due to air pollution (MDAP) and their level of control of solid waste (CSW), with COVID-19 total number of cases. This combination of predictors accounted for approximately 28% of the variance in the total number of cases. A predictive equation for the number of COVID-19 cases, within a 90% confidence interval, was created using both the MDAP and CSW: Estimated COVID-19 total cases = 10.534(MDAP) + 498321.18(CSW) – 57370.23 +/- (716905.12). Regarding the number of COVID-19 deaths, 9.6% of the variance was accounted for by MDAP. Our findings support prior studies indicating air pollution as a potential catalyst for COVID-19 spread, and to a lesser extent, mortality.

One essential mitigating strategy for dealing with respiratory viruses is via abatement of air pollution. This correlates with decreased time for the virus to circulate in denser particles of polluted air along with decreased aggravation of the respiratory system. Thus, MDAP is an effective predictor of COVID-19 cases, and to a lower degree, deaths. The positive correlation with CSW and number of cases indicates a likelihood that lockdowns throughout the world created chaos in solid waste disposal systems, most notably in nations with prior effective CSW mechanisms. Conclusions demonstrate the benefit of implementing procedures focusing on minimizing air pollution and strengthening systems to CSW. Additionally, the predictive equation can be used to anticipate where areas of increased case numbers due to novel respiratory viruses could be found, thus attenuating a descent into another global pandemic.

Keywords: hygiene hypothesis; air pollution; solid waste; COVID-19; Environmental Performance Index; WaSH mortality;

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was initially identified in Wuhan, China in December, 2019. It has since wreaked havoc on a worldwide scale causing a disproportionate amount of deaths in wealthier nations [1]. Previous experience with related coronavirus illnesses, notably Severe Acute Respiratory Syndrome (SARS) [2] of 2002-2004 and the ongoing Middle East Respiratory Syndrome (MERS) [3], has allowed scientists to rapidly identify and begin to understand the highly contagious and infectious capabilities of the newly discovered 2019 SARS-CoV-2 [4,5]. As countries around the world attempted to put stringent measures in place to limit the morbidity and mortality caused by COVID-19, scientists across the globe raced to find therapeutic solutions for those infected, along with vaccines to prevent the spread. By the end of 2020, vaccine manufacturers Pfizer-BioNTech and Moderna secured FDA Emergency Use Authorization (EUA) for the first two COVID-19 vaccines available in the US [6]. Shortly thereafter, several other pharmaceutical companies released positive clinical trial data for additional COVID-19 vaccines, with Johnson & Johnson's Janssen COVID-19 vaccine also receiving EUA in the US6. However, COVID-19 cases and deaths continued to increase due to lack of social distancing, particularly during holidays, as well as to what some called 'pandemic fatigue' [7-9]. Meanwhile, more highly transmissible variants with increased virulence have emerged at a fast pace, first identified at various locations around the world, such as in the United Kingdom, South Africa, and Brazil, for example10. Studies indicate a reduced vaccine efficacy against these newly emergent variants [10-12], thus underscoring how essential it is to identify factors that are potentially implicated in reduced COVID-19 mortality.

In a recently published commentary, the question was raised concerning whether the hygiene hypothesis applies to COVID-19 susceptibility. Sehrawat, et al argued the very real possibility that frequent exposure to pathogens and infectious agents prepares the immune system to be able to battle newer infections such as those caused by SARS-CoV-21. The hygiene hypothesis is centered around the theory that exposure to pathogens beginning in early childhood with repeated frequency allows the immune system to become more robust in combating newly acquired infections. It was initially discovered by Strachan during a study on 17,414 British children born in 1958. He discovered that there was an inverse correlation between the prevalence of hay fever and the number of older siblings [13]. This was further expanded upon in numerous studies such as the case-controlled study on early social mixing and childhood Type I Diabetes Mellitus (Type 1 DM) [14] as well as the cross-sectional study on the age of starting nursery school and the occurrence of childhood allergies [15].

The latter study concluded that early infections were protective against development of allergies later on in life in concordance with the hygiene hypothesis [15]. So what exactly is the hygiene hypothesis? The hygiene hypothesis postulates that CD4+ T Helper 1 (Th1) and CD4+ T Helper 2 (Th2) cells must be in balance for proper functioning of the immune system [9]. In developed nations, it has been seen that a decrease in pathogen exposure leads to a weaker immune system, predominated by a Th1 immune reaction that aberrantly attacks self-antigens and other allergens. This is hypothesized to be tied to the increased prevalence of autoimmune diseases, allergies, and asthma in the US [16]. Improved hygiene, use of antibiotics and vaccinations are several factors implicated in the decrease in stimulation of Th1 cells which in turn causes an increase in activation of the Th2 response. This response includes release of cytokines interleukin (IL)-4, IL-5 and IL-13 which are associated with an increase in IgE and eosinophilic responses in atopy, along with IL-10, which has an anti-inflammatory response [17]. The immunological concept of Th1 and Th2 is further displayed in Figure 1.

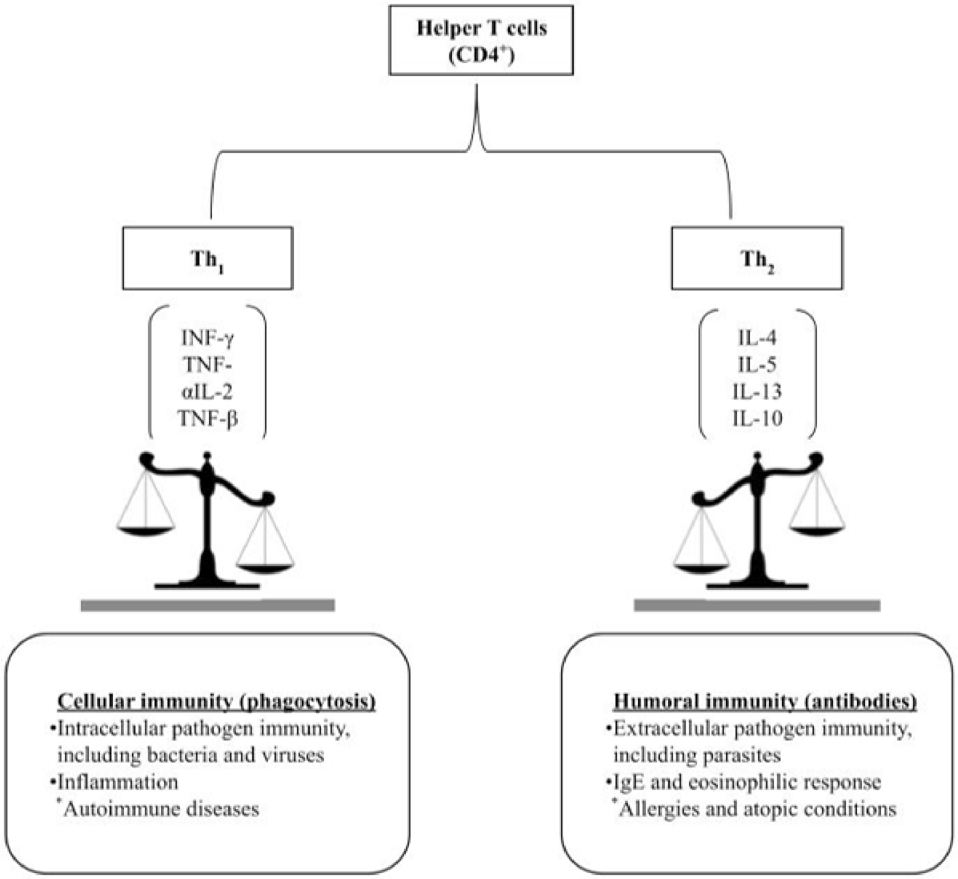

Figure 1: CD4+ Th1 and Th2 cells and their roles in immune responses. Unique characteristics of Th1 and Th2 cells are shown, including *aberrant responses when the delicate balance is disrupted.

Although the hygiene factor cannot be measured with a single numeric representation, it can be analyzed using WaSH mortality rates along with select factors from the Environmental Performance Index (EPI). The EPI is derived from a combination of 32 environmental and hygiene variables, as defined by Yale University and Columbia University in collaboration with the World Economic Forum (Supplementary Table 1) [18]. Taken together, the EPI rankings provide an indication of how nations address common environmental challenges. When exploring the individual variables, it becomes evident that many of the factors directly pertaining to the hygienic conditions of each nation would likely have a direct impact on the health and immune status of inhabitants. By extension, they may potentially play a role in an individual developing COVID-19 and/or succumbing to the disease. As the raw data for these variables were made available on the EPI website and additional factors representative of hygiene could be assessed from various public databases, in this study, we sought to expand on that assumption with analysis of available global data to determine if the hygiene hypothesis was correlated to the differences in COVID-19 cases and deaths seen in the first phase of the pandemic globally. During this phase, characterized as prior to the widespread emergence of variants of concern, it was difficult to accurately predict where surges would occur worldwide, therefore, we sought to additionally utilize these surrogate factors to determine a predictive equation, thus allowing for a multi-disciplinary approach to assess the role of the hygiene hypothesis in COVID-19 cases and deaths.

Methods

Data representing 190 nations were collected from various publicly-accessible sources. Specifically, the data included the total number of COVID-19 cases and deaths through December 28, 2020 along with the total of COVID-19 tests conducted (Johns Hopkins Coronavirus Resource Center (CRC))19. The average stringency index was calculated by finding the mean of each individual country's daily stringency index [19]. COVID-19 case fatality rate per nation was calculated using the total number of cases and deaths. Metrics pertaining to WaSH mortality were retrieved from WHO [20]. Data on mortality due to unsafe water source, unsafe sanitation, and lack of access to handwashing facilities, as well as proportion of population using limited drinking water services, limited and basic sanitation services and practicing open defecation were retrieved (UNICEF) [21]. Additional hygiene surrogate factors including mortality due to various types of air pollution such as general air pollution and solid fuels (OurWorldInData) [22], along with household and ambient air pollution (Data.worldbank) [23] were also collected. Finally, EPI itself, along with data representing 11 variables of the EPI were obtained: emission growth rate of carbon dioxide and methane; control of solid waste; air pollution from exposure to household solid fuels, fine particulate matter (PM) 2.5 and ozone; proportions of population connected to wastewater treatment and wastewater collected that is is treated; daily adjusted living years due to unsafe sanitation, unsafe drinking water and exposure to lead [18]. All raw data were organized in MS Excel version 2106 and can be found in Supplementary Table 2.

Data were analyzed via IBM SPSS version 27.0. Specifically, Spearman correlation analysis was used to determine any correlations present between the 29 factors. The correlation analysis was later converted into a heatmap in RStudio version 4.1 for easy interpretation of the factors that showed a significant correlation within the Spearman analysis. SPSS was further used to conduct multi-regression analyses to determine the combination of factors most predictive of COVID-19 total cases and deaths. The outliers, defined as those above 3 standard deviations from the mean, were removed from the analysis. Beta coefficients from the multiple regression analysis were used to derive a predictive equation for COVID-19 total cases.

Results

As a preliminary analysis to determine the number of potential predictors to include in the multiple regression, a Spearman correlation was computed. After obtaining the Spearman correlation, the following rules were used to classify the correlation strengths: very high positive correlation (0.9-1.0), high positive correlation (0.7- 0.9), moderate positive correlation (0.5 to 0.7), low positive correlation (0.3 to 0.5), and negligible correlation (0 - 0.3). Negative correlations were also given the same strength classification. All statistical analyses were considered significant if alpha was less than or equal to 0.05. The heat map translates the Spearman correlation into an easily visualized data set depicting the magnitude and direction of correlations (Figure 2).

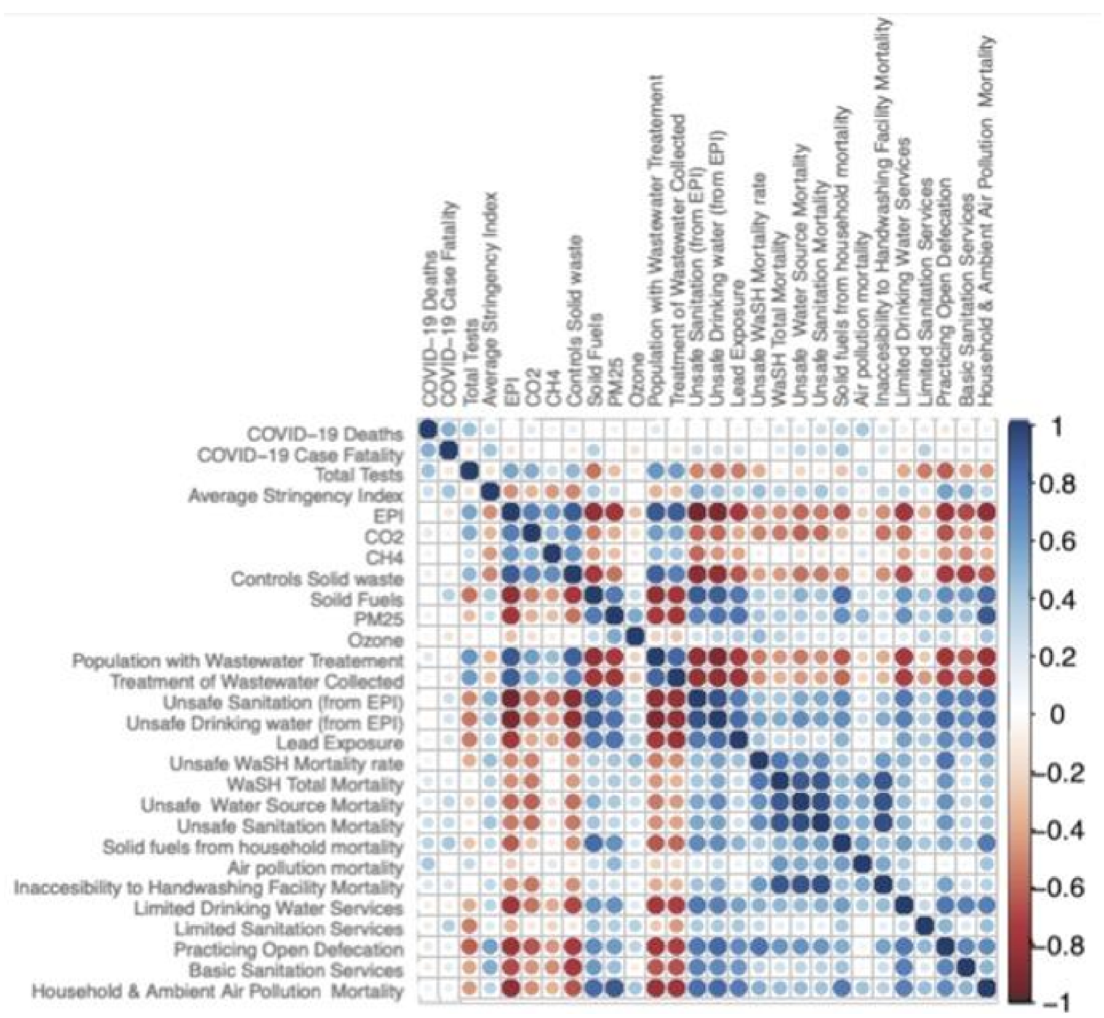

Figure 2: Heatmap of Spearman correlations to determine potential predictors of COVID-19 total cases and deaths. The direction and strength of correlations can be visualized as follows: positive and negative correlations are indicated by blue and red, respectively, while increasing strength of correlation corresponds to larger circle size.

Prior to conducting the multiple regression analysis, investigation of statistical assumptions was undertaken. The Durbin-Watson statistic was 1.742 for the COVID-19 total cases and 1.548 for the COVID-19 deaths, suggesting an absence of autocorrelation of residuals. Multicollinearity was examined using the tolerance and Variance Inflation Factor (VIF) statistics for each of the predictive variables. For COVID-19 total cases, the tolerance and VIF for mortality due to air pollution was 0.961 and 1.041, respectively, and for control of solid waste, it was 0.421 and 2.373, respectively. These were appropriate and indicated the absence of multicollinearity between predictors. In order to achieve an accurate predictive model, outliers were removed. For COVID-19 total cases, those outliers included the countries of China, USA, Brazil, Yemen, Bangladesh. Furthermore, in order to maintain the homoscedasticity, India was removed from the analysis. When investigating COVID-19 deaths, the outliers that were removed were Brazil, USA, and Mexico, and those removed to maintain homoscedasticity were China and India.

The regression model for COVID-19 total cases, using mortality due to air pollution and controlling solid waste, was found to be statistically significant, F (2, 171) = 35.11, $p < .001$, adjusted R2 = 0.283, suggesting approximately 28% of the variability in COVID-19 total cases can be accounted for by the linear combination of these two factors. Using the beta coefficients determined from the analysis, the following equation was derived to create a 90% confidence interval in predicting COVID-19 total cases:

Estimated COVID-19 total cases = 10.534(mortality due to air pollution)+498321.18(controls solid waste) - 57370.23 +/- 716905.12)

On the other hand, the regression model for COVID-19 deaths, using just mortality due to air pollution, was shown to be statistically significant, F (1, 175) = 19.77, $p < .001$, adjusted R2 = 0.096, accounting for only 9.6% of the variability in COVID-19 deaths. Furthermore, it was evident that the variables found to be significant were positively correlated with COVID-19 cases and deaths. The multi-regression analyses of COVID-19 case numbers and deaths are shown in Table 1 and Table 2, respectively.

Table 1. Multiple regression analysis of COVID-19 total cases by nation

Model Summary

					Change Statistics					
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	R Square Change	F Change	df1	df2	Sig. F Change	Durbin-Watson
1	.540[a]	.291	.283	434487.949	.291	35.110	2	171	.000	1.742

a) Predictors: (Constant), Controls Solid waste (2017), Mortality due to air pollution (2017)
b) Dependent Variable: Covid 19 Total Cases (12/28/2020)

ANOVA

Model		Sum of Square	Df	Mean Square	F	Sig.
1	Regression	1.326E+13	2	6.628E+12	35.110	.000[b]
	Residual	3.228E+13	171	1.888E+11		
	Total	4.554E+13	173			

a) Dependent Variable: Covid-19 Total Cases (12/28/2020)
b) Predictors: (Constant), Controls Solid Waste (2017), Mortality due to air pollution (2017)

Coefficients

Model		*Unstandardized B	Coefficients Std. Error	Standardized Coefficients Beta	t	Sig
1	(Constant)	-57370.231	51253.526		-1.119	.265
	Mortality due to air pollution (2017)	10.534	1.607	.422	6.553	.000
	Controls Solid waste (2017)	498321.183	90471.778	.355	5.508	.000

a) Dependent Variable: Covid 19 Total Cases (12/28/2020)

Table 1: Mortality due to air pollution and control of soli.

d waste account for 28.3% of the variability in COVID-19 total cases.

*Predictive equation: Estimated COVID-19 total cases = 10.534(mortality due to air pollution) + 498321.18(controls solid waste) - 57370.23 +/- 716905.12).

Table 2. Multiple regression analysis of COVID-19 total deaths by nation

Model Summary

					Change Statistics					
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	R Square Change	F Change	df1	df2	Sig. F Change	Durbin-Watson
2	.319[a]	.102	.096	12198.116	.102	19.774	1	175	.000	1.548

a) Predictors: (Constant), Mortality due to air pollution (2017)
b) *Dependent Variable: Covid Deaths (12/28/2020)*

ANOVA

Model		Sum of Square	Df	Mean Square	F	Sig.
2	Regression	2942234370	1	2942234370	19.774	.000[b]
	Residual	2.604E+10	175	148794034.4		
	Total	2.898E+10	176			

a) Dependent Variable: Covid Deaths (12/28/2020)
b) *Predictors: (Constant), Mortality due to air pollution (2017)*

Coefficients

		Unstandardized Coefficients		Standardized Coefficients		
Model		B	Std. Error	Beta	t	Sig.
2	(Constant)	4711.249	1111.503		4.239	.000
	Mortality due to air pollution (2017)	.061	.008	.484	7.353	.000

a) Dependent Variable: Covid Deaths (12/28/2020)

Table 2: Mortality due to air pollution accounts for 9.6% of the variability of COVID-19 total deaths.

Discussion

Multiple studies, along with media speculation, hypothesized that COVID-19 case fatality rates were lower in developing countries during their respective first phase of the pandemic due to exposure to various infectious childhood diseases that most of the population would have been exposed to, or in other words, due to the hygiene hypothesis [24]. Additional theories indicated that more frequent and numerous exposures to infectious pathogens due to decreased hygiene resulted in a more robust immune system allowing individuals to fight new and emerging diseases quickly.

The surrogate factors that explained approximately 28% of the variability seen in COVID-19 total cases, mortality due to air pollution and control of solid waste, however, were positively correlated to COVID-19 total cases. Although these factors seem unrelated to the immune system, environmental cleanliness is of the utmost importance when it comes to how easily infectious organisms, particularly a respiratory virus, can be sustained and transmitted, thus, likely elevating rates of infection.

Mortality Due to Air Pollution

Air pollution kills an estimated seven million people worldwide each year25,26.WHO data shows that 9 out of 10 people breathe air that exceeds WHO's guideline limits containing high levels of pollutants, with inhabitants of low- and middle-income countries suffering from the highest exposures [25,26]. From smog hanging over cities to smoke inside the home, air pollution poses a major threat to health and climate. The combined effects of ambient outdoor and household air pollution cause about seven million premature deaths every year, largely as a result of increased mortality from stroke, heart disease, chronic obstructive pulmonary disease, lung cancer and acute respiratory infections [25]. Our analysis suggests that nations reporting high mortality due to air pollution prior to the pandemic had higher cases of COVID-19, even though this seems to diverge from the hygiene hypothesis. This can be explained, in part, due to the fact that as more pollutant particles are present in the air, combined with an increase in the amount of denser suspended particles, the chances of viruses such as SARS-CoV-2 being able to be present and viable for a longer time suspended in air is higher than in areas with cleaner air circulation. Research has already shown that COVID-19 lasts longer and travels farther in denser atmospheric particulate matter [27].

Although not directly related to the immune aspect of the hygiene hypothesis, factors such as increased biodiversity, tree cover loss, grassland loss, and others are indirectly correlated due to their impact on air quality. Other factors, including the emission growth of carbon dioxide, methane, nitrous oxide and greenhouse gas emission are also perpetrators in increasing air pollution and decreasing air quality, thereby potentially increasing COVID-19 transmission [28]. Furthermore, deceased air quality affects the lungs and alveoli by producing inflammatory responses that create a host environment ripe for infections, as seen in individuals with compromised lungs and alveoli being more prone to respiratory infections [27]. Hence, our study reveals that populations exposed to higher air pollution had increased COVID-19 cases and deaths when analyzing the first wave of this pandemic.

As an example, Denmark is a more hygienic nation than the USA based on their EPI rankings. Additionally, when comparing their respective numbers of mortality attributable to air pollution, based on the most recently available data, Denmark only had a mortality rate of 2,366 while the USA had a mortality rate of 107,506 in the same time frame. When considering COVID-19 cases, deaths, and case fatality rates, as of December 28, 2020, Denmark had recorded 156,434 total COVID-19 cases of which there was a case fatality rate of only 0.008, while the USA had 19,301,543, with an increased case fatality rate of 0.017. Thus as expected, air pollution plays a significant role in respiratory illness transmission and further confirms the importance of minimizing pollution in our society as a tool to mitigate future respiratory outbreaks.

Controlling Solid Waste

Solid waste includes microplastics such as landfill refuse, sludge, food waste, and healthcare waste [29]. Solid waste is a major concern and cause for soil and water pollution [24,25]. During the initial COVID-19 case spikes, governments initiated city wide lockdown measures that included waste management and recycling companies. With increased waste generation from healthcare facilities, and households that had increasing numbers of family members staying home, lack of proper disposal is likely to have contributed to easier transmission of COVID-19 [30]. Research has shown that increased COVID-19 cases were correlated to improper management of solid waste, especially PPE and other healthcare waste [31].

Our analysis suggests that geographic locations with lesser control of solid waste management trended towards lower COVID-19 cases in the first phase of the pandemic. At face value, this correlation seems to support the hygiene hypothesis. However, one theory that could better explain this finding, is that individuals in nations without a well-established waste disposal system prior to COVID-19 simply continued discarding waste as they previously had. This likely included personal means of mitigating risk of infection. In contrast, countries that had previously well-functioning control of solid waste disposal systems likely had significant disruptions as they were left to figure out alternative ways to dispose of their waste due to COVID-19 lockdowns. In the USA, for example, government-assisted recycling initiatives were put on hold during the early lockdown caused by the pandemic [32], while the massive volume of discarded masks and other PPE accumulated. Similar situations likely impacted many developed countries in their race to limit social contact and spread of COVID-19.

Conclusion

COVID-19 cases and deaths both showed a significant positive correlation to mortality due to air pollution. COVID-19 cases also showed positive correlation to increased control of solid waste. These findings reiterate what other researchers have found and are a stepping stone for further research. Additional studies need to be conducted to understand the true role of controlling solid waste in causing a higher incidence of COVID-19 cases. Also, research looking at the main countries that had to be removed from further analysis are imperative to understanding exactly why the hubs of the COVID-19 pandemic were significantly different from the rest of the world.

Conflict of Interest: There were no conflicts of interest.

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