Effects of Particulate Matter Exposure on the Transmissibility and Case Fatality Rate of COVID-19: A Nationwide Ecological Study in China

Jinjun Ran[1,2†,*], Shi Zhao[3,4,†], Lefei Han[5], Yulan Qiu[2], Peihua Cao[6], Zuyao Yang[3], Marc KC Chong[3,4], Lin Yang[5], Maggie H Wang[3,4], and Daihai He[7,*]

[1] School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong Special Administrative Region, China

[2] School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China

[3] JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong Special Administrative Region, China

[4] CUHK Shenzhen Research Institute, Shenzhen, China

[5] School of Nursing, Hong Kong Polytechnic University, Hong Kong Special Administrative Region, China

[6] Clinical Research Center, Zhujiang Hospital, Southern Medical University, Guangzhou, China

[7] Department of Applied Mathematics, Hong Kong Polytechnic University, Hong Kong Special Administrative Region, China

† Jinjun Ran and Shi Zhao contributed equally.

*** Correspondence:** Daihai He, Department of Applied Mathematics, Hong Kong Polytechnic University, Hong Kong, China. E-mail: daihai.he@polyu.edu.hk; and Jinjun Ran, School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong Special Administrative Region, China. E-mail: jimran@connect.hku.hk

Authors' Contributions: J. Ran and S. Zhao conceived the study and carried out the analysis. L. Han and P. Cao collected the data. J. Ran and S. Zhao drafted the first manuscript and discussed the results. Y. Qiu, Z. Yang, M.K.C. Chong and L. Yang contributed to the interpretation of the results. M. H. Wang and D. He supervised the project. All authors critically read and revised the manuscript and gave final approval for publication.

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To the Editor

The coronavirus disease 2019 (COVID-19) pandemic has become one of the worst global health crises in the recent 50 years. Emerging studies from Italy and the United States suggested that particulate matter (PM) could impact the transmissibility and risk of death of COVID-19.[1,2] The generality of these findings remains unsettled in other regions. This study aims to examine whether the particulate matter is an environmental determinant of COVID-19 transmissibility or its crude case fatality rate (CFR) in China.

We obtained the data of COVID-19 cases and deaths for 303 Chinese cities during December 2019 - March 2020 from the Chinese provincial health agencies and China National Health Commission. The basic reproductive number (R_0) was calculated to quantify the COVID-19 transmissibility for each city by the Euler-Lotka equation,[3] with a Gamma-distributed generation interval having mean (±SD) values of 5.5 (±3.3) days.[3,4] The crude CFR was calculated as the ratio of cumulative confirmed deaths over confirmed cases during the period. Environment monitoring data during the same period of each city were obtained from the China National Environmental Center, including PM_{10} (particulate matter with an aerodynamic diameter less than 10 μm) and $PM_{2.5}$ (particulate matter with an aerodynamic diameter less than 2.5 μm). The concentration of $PM_{10-2.5}$ was calculated using PM_{10} and $PM_{2.5}$ concentration data. We then computed mean concentrations of the three PM categories during the period. City-level meteorological data were obtained from the National Meteorological Data Center. The demographic information was extracted from the China Statistical Yearbook (2019 version), including the percentage of the population age ≥ 65 years, sex ratio, percentage of the population with high education, gross domestic product (GDP) per city, and population density.

We examined the relationship between R_0s and PM concentrations by the nonlinear univariable and multivariable (adjusted for temperature and relative humidity) regression analyses. We carried out the fitting procedure with a scheme weighted by the total number of cases from each city. Then we adopted the generalized linear model with the quasi-binomial framework to estimate the associations between CFRs of COVID-19 and PM concentrations. The gradient variable adjustment, from univariable to multivariable, was performed to control potential confounders, including meteorological and demographic covariates. The risk estimates were reported as the odds ratio (OR) with corresponding 95% confidence interval (CI) in CFR per 10 $\mu g/m^3$ increase in PM concentrations. Secondary validation was conducted by repeating the analysis among cities with cumulative cases ≥ 30 and ≥ 50. Considering the number of COVID-19 death in Wuhan was modified in April 2020, we removed Wuhan city as a sensitivity analysis to test the robustness of results.

There were 154 Chinese cities being detected with the COVID-19 outbreak, and all of them were included in further analysis. The maximal R_0 was estimated at 2.5 (95%CI: 2.4−2.6) in Wuhan, which is largely consistent with previous findings.[4] At the end of March, there were 82,585 confirmed cases and 3,314 deaths for COVID-19 in China, and thus the crude CFR is 4.0%. After removing Wuhan city, the CFR is about 2.4%. A total of 132 and 83 Chinese cities had cumulative cases ≥ 30 and ≥ 50, respectively. PM_{10} concentrations ranged from 26.3 $\mu g/m^3$ to 143.1 $\mu g/m^3$ and $PM_{2.5}$ concentrations ranged from 21.4 $\mu g/m^3$ and 109.4 $\mu g/m^3$ among the included 154 Chinese cities. $PM_{2.5}$ was highly correlated with PM_{10}. The Pearson correlation coefficient was 0.96 (p value < 0.001). In the regression analysis, the relationships between COVID-19 transmissibility (R_0) and three PM categories in both univariable and multivariable models were not statistically significant (Figure 1). However, all three PM categories were positively associated with the mortality risk of COVID-19 (Table 1). Specifically, in 132 Chinese cities with confirmed cases ≥ 30, 10 μg/m^3 escalations in PM_{10}, $PM_{10\text{-}2.5}$ and $PM_{2.5}$ were positively associated with the increased risk of the crude CFR with ORs = 1.29 (95%CI: 1.14, 1.46), 1.54 (95%CI: 1.20, 1.96), and 1.28 (95%CI: 1.09, 1.51), respectively. After adjusting for meteorological and demographic covariates, the regression models explained 16.7%, 14.6%, and 14.5% variability of CFR in terms of the McKelvey & Zavoina's pseudo-R-squared. The area under the receiver operating characteristic curve (AUC) was 0.71, 0.72 and 0.70 for PM_{10}, $PM_{10\text{-}2.5}$ and $PM_{2.5}$, respectively. In addition, we did not find clear effect modification of other covariates, such as temperature,[5,6] on the PM exposure (p value > 0.05). We thus excluded the interaction terms from the main analysis. The results remained consistent after excluding Wuhan city (data not shown).

Our findings indicated that the association between PM exposure and COVID-19 transmission was not statistically evident, but PM exposure was likely to increase the mortality risk among COVID-19 infected cases. Setti *et al.* found that PM_{10} could be positively associated with the incidence of COVID-19 in Northern Italy and they hypothesized that airborne particles might serve as a carrier of pathogens [1]. However, relevant epidemiological evidence to date is still insufficient. The positive association between PM exposure and the COVID-19 CFR, observed in China, aligned with another nationwide study in the United States, where Wu *et al*. found that only 1 μg/m^3 escalation in $PM_{2.5}$ could result in a 15% increase in the COVID-19 mortality rate.[2] The findings were also in line with previous studies illustrating the relationship of air pollution with the CFRs of the severe acute respiratory syndrome (SARS) in the outbreak in 2003.[7] PM exposure may result in oxidative stress and respiratory inflammation of hosts since PM is the source of reactive oxygen species (ROS) and also elicit increased ROS generation in exposed cells.[8] Pollutant-induced ROS can potentially deplete antioxidants and trigger a series of local or systemic inflammation, which would exacerbate severe respiratory symptoms and an increased risk of death.[8] Further investigations are urgently required to evaluate the potential impacts of PM exposure on the virus itself, such as adhesion, activity, and toxicity

Cautions should be taken when interpreting the results. First, some confounders were not adjusted in this analysis, such as smoking prevalence, BMI distribution, the coverage of health insurance and local health expenditure due to data unavailability. We remarked the importance of controlling the unmeasured confounders. Our analytical framework can accommodate these confounders once they are available. Second, the prevalence of city-level comorbidities, especially cardiorespiratory diseases, could modify the association of the COVID-19 CFR with PM exposure. The prevalence might also mediate the association in partial since the PM exposure could amplify the risk of comorbidities.[9,10] However, these factors were not incorporated in the current analysis due to lack of data. Thus, the risk estimates of three PM metrics on the CFR could be only interpreted as the average total effects. Third, the ecological fallacy was inescapable, so that the population-level results cannot deduce to individuals. Fourth, we ignored the right-censoring situation in the crude CFR calculation since our study period was relatively long for infectious disease epidemics. Our analytical approach could be extended by incorporating the truncated or zeroinflated likelihood framework to address the limitation. Last, for the dataset used in our analysis, the local and imported cases could not be disentangled in each city, which might cause a noise in the R_0 estimation. Nevertheless, the noise should be minor due to the early lockdown of Wuhan.

In summary, our study observed an ecological association of city-level COVID-19's CFR with PM exposure. More studies are warranted to further examine the potential effects of PM on the transmissibility, activity, and toxicity of the COVID-19 virus.

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Table 1. Estimated associations of the COVID-19 crude CFR associated with per 10 μg/m^3 increase in the concentrations of three particulate matter categories (PM_{10}, $PM_{10\text{-}2.5}$ and $PM_{2.5}$) in multiple models.

	Sample	PM_{10}		$PM_{10\text{-}2.5}$		$PM_{2.5}$	
		OR (95%CI)	*p*-value	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
All included cities							
Model 1[†]	303	1.12 (1.04, 1.21)	0.005	1.15 (0.98, 1.34)	0.085	1.18 (1.05, 1.32)	0.006
Model 2[‡]	303	1.14 (1.03, 1.26)	0.009	1.19 (1.00, 1.42)	0.056	1.18 (1.03, 1.35)	0.020
Model 3[§]	303	1.13 (1.04, 1.22)	0.003	1.16 (1.00, 1.34)	0.048	1.21 (1.06, 1.37)	0.004
Model 4[*]	303	1.19 (1.07, 1.32)	0.001	1.24 (1.05, 1.46)	0.010	1.27 (1.08, 1.49)	0.004
Remove cities with cumulative cases < 30							
Model 1[†]	132	1.11 (1.02, 1.21)	0.014	1.14 (0.95, 1.37)	0.163	1.17 (1.03, 1.32)	0.013
Model 2[‡]	132	1.12 (1.00, 1.26)	0.050	1.18 (0.94, 1.48)	0.163	1.14 (0.98, 1.32)	0.089
Model 3[§]	132	1.17 (1.07, 1.27)	0.001	1.27 (1.06, 1.52)	0.011	1.23 (1.09, 1.40)	0.002
Model 4[*]	132	1.29 (1.14, 1.46)	<0.001	1.54 (1.20, 1.96)	0.001	1.28 (1.09, 1.51)	0.003
Remove cities with cumulative cases < 50							
Model 1[†]	83	1.10 (0.99, 1.22)	0.093	1.08 (0.83, 1.39)	0.582	1.13 (0.99, 1.29)	0.077
Model 2[‡]	83	1.09 (0.95, 1.26)	0.219	1.10 (0.83, 1.44)	0.510	1.11 (0.93, 1.33)	0.258
Model 3[§]	83	1.13 (1.02, 1.26)	0.026	1.28 (1.01, 1.64)	0.048	1.15 (0.99, 1.32)	0.065
Model 4[*]	83	1.27 (1.11, 1.45)	0.001	1.47 (1.12, 1.94)	0.007	1.26 (1.06, 1.51)	0.012

Abbreviations: CFR, case fatality rate; OR, odds ratio; 95% CI, 95% confidence interval; PM_{10}, particulate matter with an aerodynamic diameter less than 10 μm; $PM_{10\text{-}2.5}$, particulate matter with aerodynamic diameter between 2.5 and 10 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm; ER%, percent excess risk.

Model 1: univariable model; Model 2: adjusted for temperature and relative humidity; Model 3: adjusted for percentage of the population age ≥ 65 years, sex ratio, percentage of the population with high education, GDP per city, population density; and Model 4: adjusted for both meteorological and demographical covariates, including temperature, relative humidity, percentage of the population age ≥ 65 years, sex ratio, percentage of the population with high education, GDP per city, population density.

Figure 1

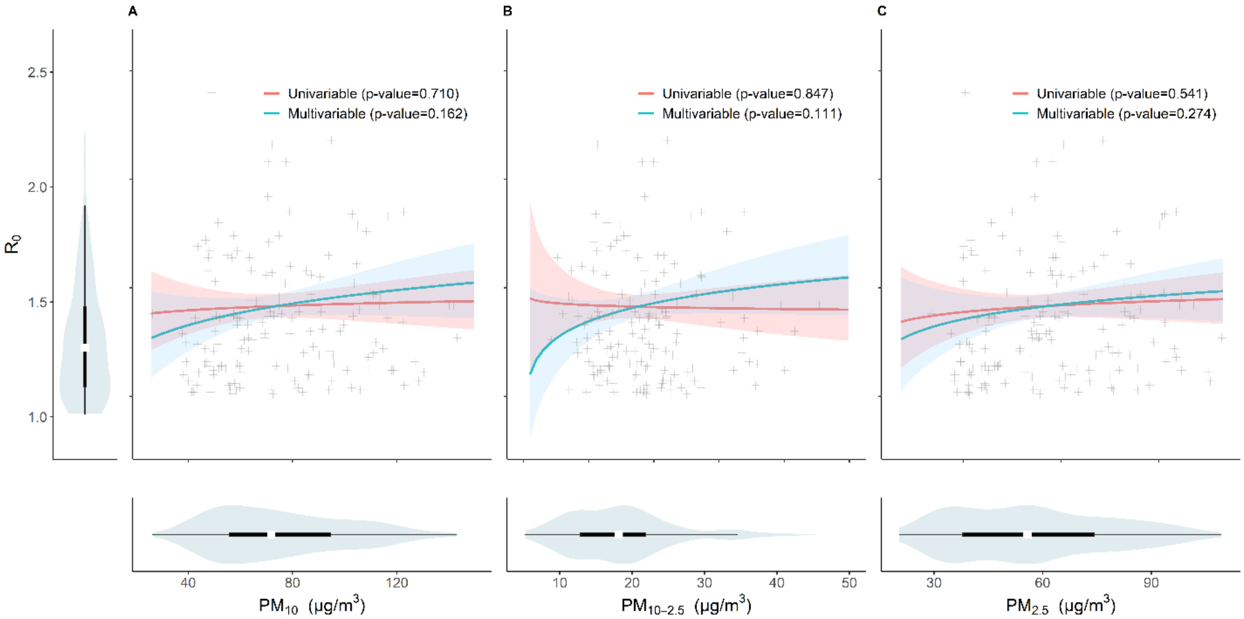

Figure 1. Estimated nonlinear relationships of the COVID-19 R_0s with PM_{10} concentrations across 154 Chinese cities. Panel A, B and C are the relationships of R_0 with PM_{10}, $PM_{10\text{-}2.5}$, and $PM_{2.5}$, respectively. The red line represents the relationship in the univariable regression, and the blue line indicates the relationship in the multivariable regression. The p-value ≥ 0.05 means the null-hypothesis is not rejected. The violin plot in the bottom represents the distribution of their concentrations and the violin plot on the left shows the distribution of R_0; their medians are indicated by the white square, their interquartile ranges are represented by the black rectangle, and the distribution of values is shown by the light-blue area.