Journal of Infection 81 (2020) e9–e11

Contents lists available at ScienceDirect

# Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

## The ambient ozone and COVID-19 transmissibility in China: A data-driven ecological study of 154 cities

*Dear Editor,*

The coronavirus disease 2019 (COVID-19) has triggered a pandemic and is still spreading around the world. Exploring the environmental factors that associate with the prevalence and transmission would improve the understanding of COVID-19 and contribute to the long-term control strategies of the outbreak.[1,2] Besides the meteorological factors[3], to what extend do common air pollutants may affect the COVID-19 transmission remains unclear. In this study, we examined the associations between common air pollutants and COVID-19 transmissibility in Chinese cities.

We obtained the daily count of COVID-19 cases for each Chinese city from the Chinese provincial health agencies and China National Health Commission (CNHC).[4] We quantified the transmissibility of COVID-19 by using the basic reproduction number ($R_0$), a unit-free measure of infectivity that is commonly used in infectious disease epidemiology. Then, we filtered out a case series of each city from the first-case occurrence to the following 16 days for estimating the $R_0$.[5] We calculated the $R_0$ for each Chinese city with a Gamma distribution having mean (±SD) values of 5.5 (±3.3) days for the serial interval averaged from previous estimations. The calculation in detail was shown in supplementary materials. As $R_0$ is a measurement regarding the population as a whole, the demographic heterogeneities across each city could be thus neglected.

We obtained air pollutants monitoring data in 1642 stations from China National Environmental Center between December 10, 2019 and February 29, 2020, including ozone ($O_3$) with three metrics – daily average, daily 1-h maximum, and daily 8-h maximum, as well as other criteria pollutants. After calculating their average values across the time period, we computed a raster for each pollutant by the kriging interpolation. We then extracted and linked pollutants' values to each Chinese city. The spatial distribution of $O_3$ (1-h maximum) was shown in Fig. 1A. The corresponding meteorological factors were addressed and matched by the same method. We adopted the nonlinear (i) univariable, and (ii) multivariable, i.e., adjusted by temperature and absolute humidity, regression analyses to explore the association between $R_0$ and each pollutant. We carried out the fitting procedure considering two weighting schemes that are (i) equal-weighted, and (ii) weighted by the total number of cases in each city. In addition, we employed the spline regression and permutation and perturbation analysis as sensitivity analysis for validation.

A total of 154 Chinese cities were detected with the COVID-19 outbreak ($R_0 > 1$) and were included in the regression analysis. The maximal $R_0$ was estimated at 2.5 (95%CI: 2.4 , 2.6) in Wuhan (Table 1), which is largely consistent with previous estimates.[6,7] Their spatial distribution was shown in Fig. 1B. We found that the $R_0$ of COVID-19 was negatively associated with the daily 1-h maximum $O_3$ concentration for both univariable and multivariable analyses and both weighting schemes significantly and consistently (Fig. 1C and Fig. S1). By contrast, associations with other pollutants failed to reach statistical significance. The average concentration of daily 1-h maximum $O_3$ across the 154 cities has a median at 73.1 μg/m$^3$ and ranges from 51.6 μg/m$^3$ to 106.7 μg/m$^3$ (Table 1). The Spearman's ranked correlation coefficient between daily 1-h maximum $O_3$ and $R_0$ was −0.21 (95% CI: −0.33, −0.02) (Table S1). We estimated that the ambient $O_3$ could solely explain 7.6% of the variation in the $R_0$ of COVID-19 in terms of McFadden's pseudo-R-squared for the univariable analysis, and this term increased to 9.3% in the multivariable analysis. A similar protective association between $O_3$ and the transmissibility of influenza was found in a previous study.[8] The spline regression validated the negative association (Fig. S2), and the permutation and perturbation tests represented that the observed relationship was unlikely due to chance.

To our best knowledge, this is the first study on the association of COVID-19 transmissibility with ambient ozone. The ambient ozone was associated with the reduction of COVID-19 transmission, which is probably due to its virucidal activity and possible impact on host defense. Ozone gas is highly effective in broad-spectrum disinfection and sterilization against many respiratory infections, such as SARS-CoV-1 and influenza viruses.[9] Ozone-primed immunity against viral infection might also play a critical role in the reduction of COVID-19 infectivity. Specifically, exposure to ambient ozone may trigger slight allergic reactions to human, which could enhance pulmonary innate immunity. Ozone-induced interleukin (IL)-33 is able to activate internal Th1 and CD8 T-cell reactions, which drives protective immunity against viral infections. The IL-33 is thus utilized as an adjuvant in influenza vaccines to stimulate antigen-specific immunoreactions in preclinical settings.[10,11] However, the negative association was identified merely with the 1-h maximum ozone concentration, which implied that ambient ozone may result in the wane of COVID-19 transmissibility when its concentration reached a certain threshold. Further studies are needed to explore the dose-response relationship between ozone and COVID-19 transmissibility and to infer the threshold dose of ozone concentration.

Some limitations should be noted. First, the daily 1-h maximum ozone only covered 7.6% of the transmissibility variation since the majority of the variance would be explained by the virus-intrinsic factors. Relevant intervention would be restricted though the modest effect could still modify the size of a single outbreak or a local epidemic.[8,12] Second, the imported and local cases in each city cannot be disentangled, which might introduce a constant and uniform impact on estimation of $R_0$ across cities. However, the proportion of the imported cases was expected to be small and had limited effect since the local government of Wuhan

https://doi.org/10.1016/j.jinf.2020.07.011

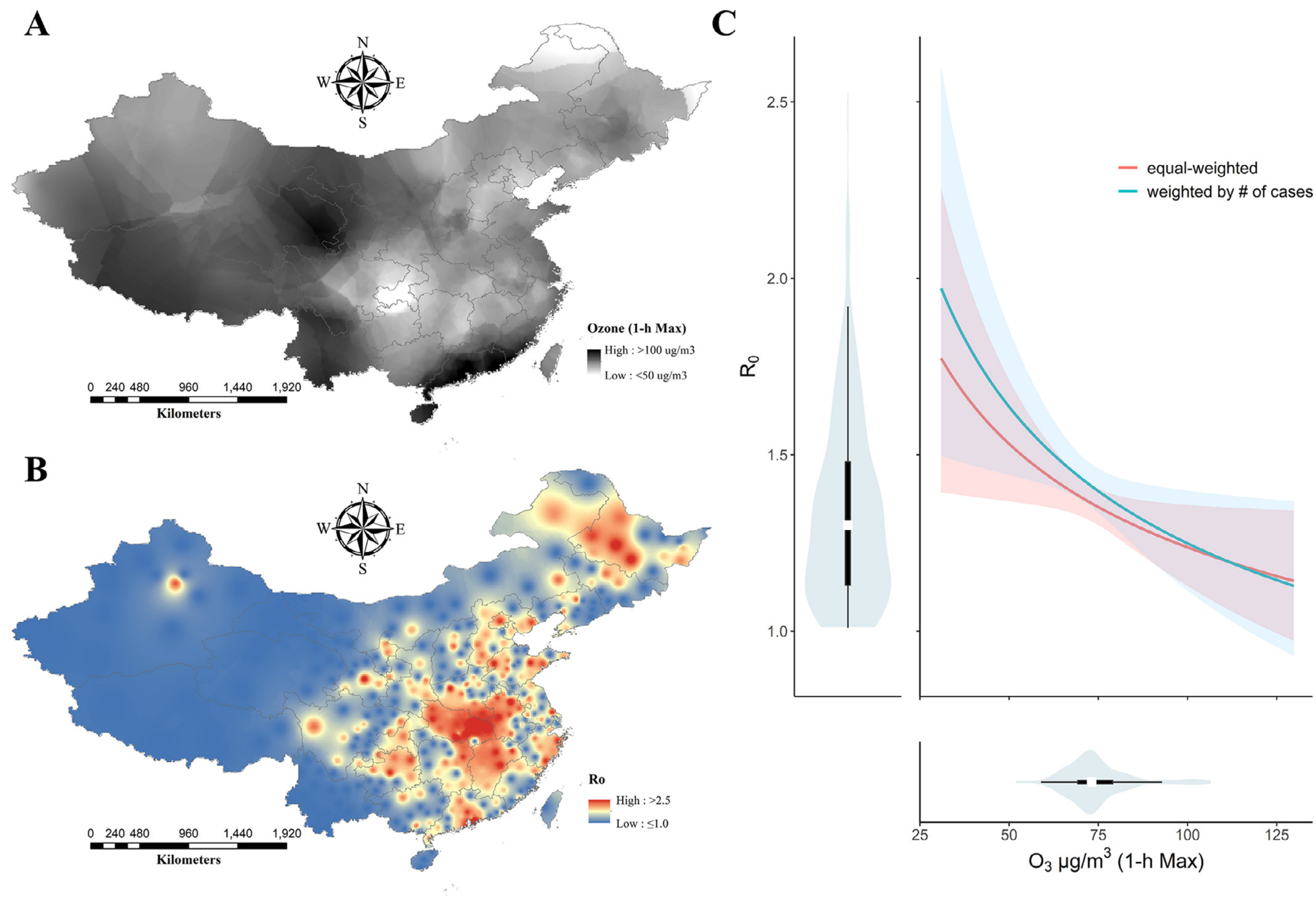


**Fig. 1.** (A) Varying levels of mean concentrations of daily 1-h maximum ozone from December 10, 2019 to February 12, 2020 by spatial interpolation with inverse distance weighting. (B) Spatial distribution of basic reproductive number ($R_0$) across 154 Chinese cities. (C) Estimated nonlinear relationships and corresponding confidence intervals between the $R_0$ and daily 1-h maximum ozone concentrations in the multivariable regression analysis with two weighting schemes (equal-weighted and weighted by the number of cases). The violin plot on the left of the panel C indicates the distribution of $R_0$, and the violin plot at the bottom shows the distribution of ambient 1-h maximum ozone concentrations; their interquartile ranges are represented by the black rectangle, their medians are indicated by the white square, and the distribution of values was shown by the light-blue area.

**Table 1**
Descriptive statistics for the basic reproductive numbers ($R_0$), three ozone metrics and weather conditions across 154 Chinese cities.

| | Mean | SD | Min | 25th | 50th | 75th | Max | IQR |
|---|---|---|---|---|---|---|---|---|
| COVID −19 transmissibility | | | | | | | | |
| $R_0$ | 1.4 | 0.3 | 1.0 | 1.1 | 1.3 | 1.5 | 2.5 | 0.4 |
| $O_3$ metrics (μg/m$^3$) | | | | | | | | |
| Daily average | 43.9 | 7.4 | 27.1 | 38.6 | 43.2 | 48.3 | 71.7 | 9.6 |
| 1-h Maximum | 75.1 | 10.5 | 51.6 | 69.2 | 73.1 | 79 | 106.7 | 9.7 |
| 8-h Maximum | 48.3 | 7.7 | 30.1 | 42.4 | 47.8 | 52.9 | 77.1 | 10.5 |
| Weather conditions | | | | | | | | |
| Temperature ( °C) | 4.3 | 8.3 | −22.5 | 0.4 | 6.2 | 9.3 | 19.1 | 8.9 |
| AH (g/m$^3$) | 7.2 | 3.9 | 0.7 | 4.2 | 7.4 | 9.4 | 18.7 | 5.2 |

Abbreviation: $R_0$, basic reproductive number; $O_3$, ozone; AH, absolute humidity; SD, standard deviation; Min, minimum value; Max, maximum value; IQR, interquartile range.

suspended all inbound and outbound transportations in the early stage, and most of the transmission occurred locally within each city.

Two implications of the current study were emphasized here. First, with the increasing temperature in the Northern hemisphere, the ambient ozone concentration in many places will gradually escalate, and this could be a good sign for the COVID-19 control regionally. Second, as a highly reactive oxidant air composition, ground-level ozone is also a "double-edged sword" to public health. We advocate more attention on the good side of ambient ozone and the trade-off of ambient ozone control to avoid over-vigilance.

## Authors' contributions

J. Ran and S. Zhao conceived the study and carried out the analysis. L. Han and D. Chen collected the data. J. Ran and S. Zhao drafted the first manuscript and discussed the results. All authors critically read and revised the manuscript and gave final approval for publication.

## Declaration of Competing Interest

D. He received support from an Alibaba (China) Co. Ltd. Collaborative Research project.

## Ethics approval and consent to participate

The COVID-19 cases data were collected via public domain [4], and thus neither ethical approval nor individual consent was applicable.

## Availability of materials

All data used in this work were publicly available [4].

## Consent for publication

Not applicable.

## Funding

D. He was supported by General Research Fund (Grant Number 15205119) of the Research Grants Council (RGC) of Hong Kong, China and an Alibaba (China) Co. Ltd. Collaborative Research project.

## Disclaimer

The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.07.011.

## References

1. Frontera A, Martin C, Vlachos K, Sgubin G. Regional air pollution persistence links to covid19 infection zoning. *J Infect* 2020.
2. Daraei H, Toolabian K, Kazempour M, Javanbakht M. The role of the environment and its pollution in the prevalence of COVID-19. *J Infect* 2020:4–5.
3. Yao Y, Pan J, Liu Z, et al. No Association of COVID-19 transmission with temperature or UV radiation in Chinese cities. *Eur Respir J* 2020. doi:10.1183/13993003.00517-2020.
4. Wu T, Ge X, Yu G, Hu E. Open-source analytics tools for studying the COVID-19 coronavirus outbreak. *medRxiv* 2020 2020.02.25.20027433.
5. Luo W, Majumder MS, Liu D, et al. The role of absolute humidity on transmission rates of the COVID-19 outbreak. *medRxiv* 2020. doi:10.1101/2020.02.12.20022467.
6. Zhao S, Lin Q, Ran J, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: a data-driven analysis in the early phase of the outbreak. *Int J Infect Dis* 2020;**92**:214–17.
7. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med* 2020;**382**:1199–207.
8. Ali ST, Wu P, Cauchemez S, et al. Ambient ozone and influenza transmissibility in Hong Kong. *Eur Respir J* 2018;**51**. doi:10.1183/13993003.00369-2018.
9. Elvis AM, Ekta JS. Ozone therapy: a clinical review. *J Nat Sci Biol Med* 2011;**2**:66–70.
10. Villarreal DO, Weiner DB. IL-33 isoforms: their future as vaccine adjuvants? *Expert Rev Vaccines* 2015;**14**:489–92.
11. Mathews JA, Krishnamoorthy N, Kasahara DI, et al. IL-33 drives augmented responses to ozone in obese mice. *Environ Health Perspect* 2017;**125**:246–53.
12. Dushoff J, Plotkin JB, Levin SA, Earn DJD. Dynamical resonance can account for seasonality of influenza epidemics. *Proc Natl Acad Sci U S A* 2004;**101**:16915–16.

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

Shi Zhao[1]
*JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong Special Administrative Region, China*
*CUHK Shenzhen Research Institute, Shenzhen, China*

Lefei Han
*School of Nursing, Hong Kong Polytechnic University, Hong Kong Special Administrative Region, China*

Dieyi Chen
*Department of Global Health, School of Health Sciences, Wuhan University, Wuhan, China*

Zuyao Yang
*JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong Special Administrative Region, China*

Lin Yang
*School of Nursing, Hong Kong Polytechnic University, Hong Kong Special Administrative Region, China*

Maggie H Wang
*JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong Special Administrative Region, China*
*CUHK Shenzhen Research Institute, Shenzhen, China*

Daihai He*
*Department of Applied Mathematics, Hong Kong Polytechnic University, Hong Kong Special Administrative Region, China*

*Corresponding author.
*E-mail addresses:* jimran@connect.hku.hk (J. Ran), le-fei.han@connect.polyu.hk (L. Han), zyang@cuhk.edu.hk (Z. Yang), l.yang@polyu.edu.hk (L. Yang), maggiew@cuhk.edu.hk (M.H. Wang), daihai.he@polyu.edu.hk (D. He)

[1] Jinjun Ran and Shi Zhao contribute equally, and thus they are considered as joint first authors.