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Association between coronavirus disease 2019 (COVID-19) and long-term exposure to air pollution: evidence from the first epidemic wave in China

--Manuscript Draft--

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Abstract:	People with chronic obstructive pulmonary disease, cardiovascular disease, or hypertension have a high risk of developing severe coronavirus disease 2019 (COVID-19) and of COVID-19 mortality. However, the association between long-term exposure to air pollutants, which increases cardiopulmonary damage, and vulnerability to COVID-19 has not yet been fully established. We collected data of confirmed COVID-19 cases during the first wave of the epidemic in mainland China. We fitted a generalized linear model using city-level COVID-19 cases and severe cases as the outcome, and long-term average air pollutant levels as the exposure. Our analysis was adjusted using several variables, including a mobile phone dataset, covering human movement from Wuhan before the travel ban and movements within each city during the period of the emergency response. Other variables included smoking prevalence, climate data, socioeconomic data, education level, and number of hospital beds for 324 cities in China. After adjusting for human mobility and socioeconomic factors, we found an increase of 37.8% (95% confidence interval [CI]: 23.8%–52.0%), 32.3% (95% CI: 22.5%–42.4%), and 14.2% (7.9%–20.5%) in the number of COVID-19 cases for every 10-μg/m ^{3} increase in long-term exposure to NO_2, $PM_{2.5}$, and PM_{10}, respectively. However, when stratifying the data according to population size, the association became non-significant. The present results are derived from a large, newly compiled and geocoded repository of population and epidemiological data relevant to COVID-19. The findings suggested that air pollution may be related to population vulnerability to COVID-19 infection, although the extent to which this relationship is confounded by city population density needs further exploration.
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Response to Reviewers:	

Dear editor, Environmental Pollution

We are submitting our manuscript entitled **"Association between coronavirus disease 2019 (COVID-19) and long-term exposure to air pollution: evidence from the first epidemic wave in China"** for your kind consideration of its suitability for publication in *Environmental Pollution*. We have an intimate understanding on the aims and scope of this journal and believe our manuscript will meet your requirements.

To the date, more than 103 million people had contracted with coronavirus COVID-19 since the disease was first identified in Wuhan. Recent reports suggested that the polluted ambient air might positively worsen the respiratory symptoms of this disease thus increase the risk of severe outcomes. Consider the negative affect of long term air pollution on lung and airway damage, which contributed to increased risk on pneumonia and influenza, we explored that chronic exposure might related with potential infectious vulnerability on COVID-19.

Our study provided evidence on explaining the relationship between COVID-19 and historical air pollution exposure, relying on a city-level database from China. In order to adjusted the confounding factor on the epidemic on infectious disease, such as the community mobility and social distancing, we considered variables like travel from Wuhan and outdoor activities to estimate the effect of air pollutants. Results showed that the elevated level of NO_2 and $PM_{2.5}$ in the past five years correspond to an increase in the number of COVID-19 cases and severe infections.

We assure that the manuscript is an original work, has not been previously published and is not under considered for publication elsewhere. All authors have read the manuscript and agree that the work is ready for submission to the journal.

Best regards,

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February 1, 2021

Dear Professor Chen
Editor, Environmental Pollution,

We appreciated to receive the comments from the referees. We have carefully revised our manuscript [ENVPOL-D-20-02781R1] according to the suggestions made by the referees and answer their questions one by one as clear as possible.

Editor and Reviewer comments:

Editor:

1. As pointed out by one of the reviewers, the current version still contains a number of grammatical problems. The authors are suggested to seek assistance from professional editing service or native English speakers.

Response: Thank you very much for the suggestions. We have sought the help of a native English speaker to check the English language carefully and avoid grammatical problems in the revised manuscript. Please refer to the revised version for details.

Reviewer #3:

1. I appreciate the effort the authors have put into the revision. There still remain many English language errors that need to be fixed throughout the manuscript. The authors have addressed most of my initial comments adequately. However, I do not believe they have fully addressed one of my central critiques. This is regarding the confounding effect of population size and density. Bigger cities with higher population densities cause more pollution but also will have more COVID-19 cases because of the population size. The Fig. 3 A, B and C show that when the authors split the dataset by city population size, the significant effect of long-term pollution disappears - the 95% confidence intervals cross the zero mark on the y-axis. This shows how population size is a

confounder in the analysis and this needs to be stated more clearly. I note places where this can be done below.

Response: Thank you very much for your comments. We appreciate the comments of the reviewer and make corresponding amendments accordingly. Meanwhile, we have checked the English language carefully to avoid grammatical errors and improve the expression to make it easier for readers to understand. At the same time, we try to explain the confounding effect of population size in our study. Please refer to the revised version for details.

2. Highlights: the first highlight needs to be re-worded. Replace "vulnerability of COVID-19" with "COVID-19 case numbers". The last highlight should change as well in my opinion. It should read something like "The association may be confounded by city population size and density"

Response: Thank you very much for your suggestions. We agree to revise the Highlights according to the reviewer's suggestion. In the revised manuscript, the first and last highlights have been modified.

3. L42: Replace "that" with "a"

Response: This sentence has been revised.

4. L44: I strongly recommend this sentence be replaced with "However, when stratifying the data by population size classes, the association became insignificant."

Response: Thank you very much for your suggestion. In the revised manuscript, this sentence has been modified.

5. L46: I strongly recommend you change your last two sentences to: "The findings suggested that air pollution may be related to the population vulnerability to COVID-19, although the extent to which this relationship is confounded by city population density needs further exploration".

Response: Thank you very much for your suggestion. In the revised manuscript, the last two sentences in the Abstract section have been modified according to the reviewer's suggestion.

6. L253-256: This is not a satisfactory presentation of the results on city population size effect. I argue that you need to state that there was no significant effect of long-term pollution on COVID-19 vulnerability when the data was stratified into population sizes. This shows how important population is as a confounding variable in the analysis.

Response: Thank you very much for your comments. We agree to revise these sentences and add the reviewer's suggestion in the Results section.

7. L322: Please do not use terms like "more obvious" which require subjective interpretation. Please be specific - was it significant or not? By looking at Fig. 3, the significance breaks down when you split the data into population size groups.

Response: Thank you very much for your comments. We added sentences to describe the impact. Sentences were revised as: There was no significant effect of long-term exposure to most of the air pollutants on susceptibility to COVID-19 infection when the data were stratified by population size. While, the effect persisted after stratification in NO_2 and $PM_{2.5}$ on confirmed COVID-19 cases among large cities and small cities, and the impact of PM_{10} in severe COVID-19 cases among large cities.

8. L358: "Fine air quality" is not a good descriptor. Please rephrase to something like "Improved air quality".

Response: Thank you very much for your suggestion. We have rephrased "Fine air quality" to “Improved air quality”.

Reviewer #4:

1. The authors have addressed more or less most of my comments. Nevertheless for some of them the aswers should be in the main manuscript and not as an answer to the point by point reply, since in my eyes these are natural questions that are generated as reading the manuscript, for instance comment 2.2, 2.4 and 3.4.

Response: Thank you very much for your comments. Indeed, some of the content we only reflected in the point by point reply, and not explicitly put in the main manuscript. In this revised version, we have modified the corresponding content. For comment 2.2, we have supplemented the corresponding information in the end of Methods 2.1 section. For comment 2.3, we have supplemented in the 4th paragraph of Discussions section. For comment 3.4, we have supplemented in the Methods 2.5 section. Please refer to the revised version for details.

2. Reading the updated version of the manuscript there are still typos and language problems, for instance line 66 induces instead of induce, line 82 trend instead of tend, line 103 consider instead of considering to name a few. I would thus suggest either the advice of a scientific writter or from a native speaker to improve the language quality of the paper.

Response: Thank you very much for your suggestions. The errors pointed out by the reviewer have been corrected. Meanwhile, we have sought the help of a native English speaker to check the English language carefully in the whole revised manuscript.

3. Also the authors havent addresed my comment about the city specific random effect, see comment 2.3. Have you repeated the analysis by adding a random effect on the city level?

Response: Thank you very much for your comments. A linear mixed effects model was established with population as the random intercept, to examine the relationship of air pollutants and COVID-19 cases. As the table shown below, NO_2, $PM_{2.5}$ and PM_{10} have effect on the confirmed COVID-19 cases in different approach, and the random effects of population could explain 63%, 52% and 66% of the variances.

Table 1 Linear mixed effects model on air pollutants and confirmed COVID-19 cases

Parameter	NO_2	$PM_{2.5}$	PM_{10}
Random effects			
Population(Intercept)-Variance	0.240	0.201	0.246
Residual-Variance	0.142	0.179	0.164
Fixed effects			
Estimate	0.773	0.135	0.034
Std.Error	0.117	0.025	0.014
P value	<0.001	<0.001	0.017

4. From the methodological perspective, it is a bit worrysome that the authors did not include population as an offset (denominator). Then all the results are confounded with population trends. Maybe the severe collinearity stems from this. Have you performed the analysis using population as an offset?

Response: Thank you very much for your comments. Additional analysis has been added as suggested using population as an offset in our model. We are happy to report that the trend of our results is consistent with our original ones. The impact of long-term exposure to NO_2, $PM_{2.5}$ and PM_{10} still reminds in our results, which indicated the results are relatively stable. While, there is no significant effect of long-term pollution on COVID-19 vulnerability when using the severe cases. The reason could be in the first wave of COVID-19 in China, as a novel infectious disease, the diagnostic capacities were limited, which explained in the fourth paragraph of discussion.

Table 2 Impact of historical air pollution exposure on cases of COVID-19 with population as the offset

Covariates	Coefficient (95%CI)	std	P
NO_2	0.198（0.18,0.216）	0.009	<0.001
Intercept	-1.74（-1.97,-1.514）	0.116	<0.001
Inflow from Wuhan	0.006（0.006,0.007）	0.000	<0.001
Within-city movements	-1.253（-1.284,-1.222）	0.016	<0.001
Peak of inflow from Wuhan	0.197（0.191,0.202）	0.003	<0.001
Mean temperature of coldest quarter	-0.030（-0.033,-0.027）	0.001	<0.001
Relatively humidity	0.046（0.044,0.049）	0.001	<0.001
Illiteracy rate	0.0506（0.046,0.056）	0.003	<0.001
$PM_{2.5}$	0.202（0.189,0.216）	0.007	<0.001
Intercept	-3.837（-4.056,-3.619）	0.112	<0.001
Inflow from Wuhan	0.006（0.005,0.006）	0.000	<0.001
Within-city movements	-1.458（-1.49,-1.426）	0.016	<0.001
Peak of inflow from Wuhan	0.218（0.212,0.224）	0.003	<0.001
Mean temperature of coldest quarter	-0.029（-0.032,-0.026）	0.002	<0.001
Relatively humidity	0.058（0.056,0.061）	0.001	<0.001
Illiteracy rate	0.048（0.043,0.053）	0.003	<0.001
PM_{10}	0.101（0.093,0.109）	0.004	<0.001
Intercept	-1.843（-2.066,-1.621）	0.113	<0.001
Inflow from Wuhan	0.006（0.006,0.006）	0.000	<0.001
Within-city movements	-1.383（-1.414,-1.352）	0.016	<0.001
Peak of inflow from Wuhan	0.180（0.175,0.186）	0.003	<0.001
Mean temperature of coldest quarter	-0.021（-0.024,-0.018）	0.002	<0.001
Relatively humidity	0.053（0.05,0.055）	0.001	<0.001
Illiteracy rate	0.045（0.04,0.05）	17.527	<0.001

Best regards,

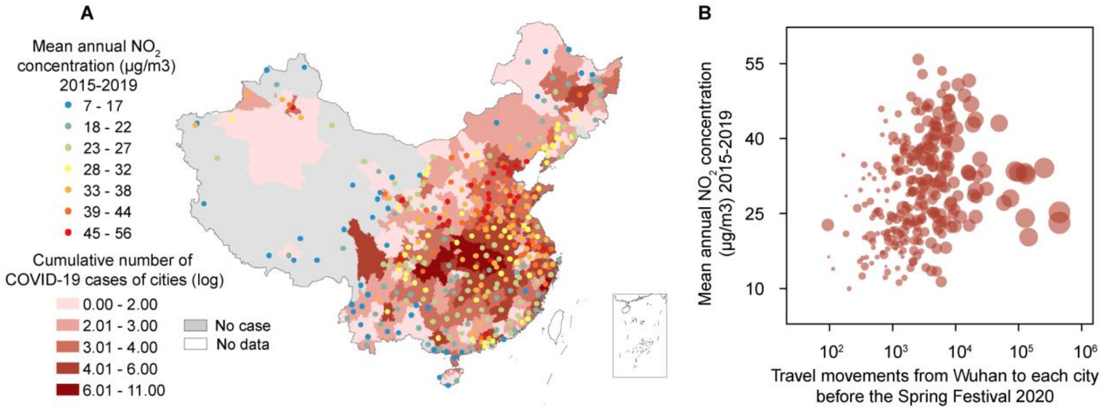
Sincerely yours

Prof. Guang Jia

Highlight

- Long-term exposure to NO_2, $PM_{2.5}$ or PM_{10} corresponded to COVID-19 case numbers.
- This study focused on the period in the first wave of China.
- The nationwide COVID-19 cases and severe infections in 324 cities of China were included.
- The association may be confounded by city population size and density

Graphical Abstract



Association between coronavirus disease 2019 (COVID-19) and long-term exposure to air pollution: evidence from the first epidemic wave in China

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Abstract

People with chronic obstructive pulmonary disease, cardiovascular disease, or hypertension have a high risk of developing severe coronavirus disease 2019 (COVID-19) and of COVID-19 mortality. However, the association between long-term exposure to air pollutants, which increases cardiopulmonary damage, and vulnerability to COVID-19 has not yet been fully established. We collected data of confirmed COVID-19 cases during the first wave of the epidemic in mainland China. We fitted a generalized linear model using city-level COVID-19 cases and severe cases as the outcome, and long-term average air pollutant levels as the exposure. Our analysis was adjusted using several variables, including a mobile phone dataset, covering human movement from Wuhan before the travel ban and movements within each city during the period of the emergency response. Other variables included smoking prevalence, climate data, socioeconomic data, education level, and number of hospital beds for 324 cities in China. After adjusting for human mobility and socioeconomic factors, we found an increase of 37.8% (95% confidence interval [CI]: 23.8%–52.0%), 32.3% (95% CI: 22.5%–42.4%), and 14.2% (7.9%–20.5%) in the number of COVID-19 cases for every 10-μg/m^3 increase in long-term exposure to NO_2, $PM_{2.5}$, and PM_{10}, respectively. However, when stratifying the data according to population size, the association became non-significant. The present results are derived from a large, newly compiled and geocoded repository of population and epidemiological data relevant to COVID-19. The findings suggested that air pollution may be related to population vulnerability to COVID-19 infection, although the extent to which this relationship is confounded by city population density needs further exploration.

Main Finding

This research reported a national-level association with long-term exposure to air pollutants and COVID-19 cases covering 324 cities in China.

Key words

Coronavirus disease 2019; COVID-19; Air pollution; Chronic exposure

Introduction

Coronavirus disease 2019 (COVID-19) has rapidly spread across the world. To date, the virus that causes COVID-19, severe acute respiratory disease coronavirus 2 (SARS-CoV-2), has infected more than 103 million people and led to approximately 2.23 million fatalities, according to John Hopkins University. Currently, several reports suggest that air pollution is associated with an increased risk of death or severe illness among people with COVID-19 infection (Magazzino, Mele et al. 2020, Wu, Nethery et al. 2020, Yao, Pan et al. 2020, Travaglio, Yu et al. 2021), on the basis of a biologically plausible pathway that might lead to serious deterioration (Conticini, Frediani et al. 2020, Frontera, Cianfanelli et al. 2020). SARS-CoV-2 can induce respiratory distress, so individuals with a compromised respiratory system are expected to be more vulnerable to infection (Qu, Li et al. 2020), and people with pre-existing conditions are more vulnerable to severe infection. A meta-analysis showed that chronic obstructive pulmonary disease (COPD), cardiovascular disease, and hypertension are associated with severe COVID-19 infection and admission to the intensive care unit (ICU) (Jain and Yuan 2020).

Long-term exposure to air pollution affects lung function and is associated with the risk of many lung diseases, including an increased prevalence of COPD, acute lower respiratory illness, and lung cancer (Götschi, Heinrich et al. 2008, Lelieveld, Evans et al. 2015, Doiron, de Hoogh et al. 2019, Liu, Chen et al. 2019). Moreover, recent research has put forth potential biological mechanisms of alveolar angiotensin-converting enzyme 2 (ACE-2) and population susceptibility to COVID-19 infection (Paital and Agrawal 2020). Additionally, chronic lung exposure to pollutants may lead to injury owing to pulmonary damage from oxidative stress, macrophage disfunction, and a disrupted epithelial barrier, thereby increasing susceptibility of the upper airways (Ciencewicki and Jaspers 2007, Frontera, Cianfanelli et al. 2020, Zhu, Xie et al. 2020). This implies that long-term exposure might increase vulnerability to lung diseases, thereby affecting the risk of COVID-19 infection in the whole population. However, recent studies tend to ignore the broad implications of long-term effects on the lungs. Furthermore, few studies have considered the important role of human travel and movement in the spatial spread of COVID-19, which might serve as a critical confounding variable in evaluating the effects of air pollution. We must understand the impact of air pollution exposure on COVID-19 infection and disease severity (Villeneuve and Goldberg 2020) in the general public, to help improve future modeling and disease burden calculations in countries around the world.

During the first epidemic wave of COVID-19 in China, to prevent further dissemination of the disease, officials in Wuhan prohibited all transport in and out of the city on 23 January 2020. In the following days, cities across mainland China launched the highest level emergency response and were able to control the epidemic outside of Wuhan by 6 March 2020. These measures substantially reduced air pollution, as confirmed by a significant reduction in pollution levels observed across cities in China between January and March 2020 (Chen, Wang et al. 2020, Villeneuve and Goldberg 2020). These data from Chinese cities (excluding Wuhan) were ideal to assess the relationship between long-term average air pollution exposure and COVID-19 risk because these cities had widely distributed COVID-19 cases and highly variable historical air quality, which had been comprehensively surveyed under consistent criteria and data standards across the country. Air pollution produces both acute and long-term health effects, so a reduction in air pollution levels can serve as a natural experiment in how to offset potential acute effects of air pollution.

Considering the proven link between air pollution and the high risk of severe COVID-19 infection, we suspected that long-term exposure to air pollutants, which increases cardiopulmonary damage, would be associated with increased vulnerability to COVID-19. To test this hypothesis, we identified sociodemographic and behavioral confounders through a literature search. We first investigated the effect of travel and movement from Wuhan city, the location where COVID-19 was first recorded and from where it spread across China. During the Spring Festival holiday in 2020, approximately 4.3 million people traveled from Wuhan to other cities in China (Tian, Liu et al. 2020). These travel patterns were strongly associated with the total number of cases reported in each city, suggesting that the outbreaks across China were mainly seeded in Wuhan city.

Methods

Epidemiological and demographic data

We collected epidemiological data from official reports of the health commissions of 324 cities, excluding Wuhan (Table 1). These included daily reports from 31 December 2019 to 6 March 2020, but excluded newly reported, locally acquired infections. Data on the proportion of severe COVID-19 cases were obtained from official reports of Provincial Health Committees and used to interpolate the city-level values. The National Health Commission of the People's Republic of China defined uniform diagnosis and treatment criteria of "2019 novel coronavirus pneumonia", to measure the number of outbreaks. The reporting system was supported by local health-related departments, including hospitals and Centers for Diseases Control and Prevention (CDCs) at the provincial or county level (Zanin, Xiao et al. 2020). In the first wave of the COVID-19 epidemic, these local CDCs sought to detect the largest possible number of infections, but people with a fever and a travel history to Wuhan were the priority groups for testing. Socioeconomic data, including the gross domestic product (GDP) per capita and number of hospital beds, were obtained from the China City Statistical Yearbook 2019. The age structure and illiteracy rate of people aged 15 years and older in each city were obtained from the Sixth National Population Census of the People's Republic of China, which was conducted by the National Bureau of Statistics of People's Republic of China in 2013. The prevalence of smoking and secondhand smoking among non-smokers was obtained from the Chinese National Nutrition and Health Survey (Wu, Huxley et al. 2008, Xia, Zheng et al. 2019). These were ecological and not individual data, which did not involve personal information; therefore, an ethics review was not required.

Human mobility data

Human movements were tracked using mobile phone data from Baidu location-based services and telecommunications operators (Table 1). The number of recorded movements from Wuhan to other cities across China was calculated from 11 to 23 January 2020. On 23 January, movements from Wuhan dropped to nearly zero because of the travel ban. Movements within each city were recorded daily until 6 March. The within-city movement index was extracted from the same operators and was measured, to reflect the average times people traveled from their location inside each city every day. This database was developed to describe people's compliance with physical distancing policies, which included suspending intracity public transport, closing entertainment venues, and banning public gatherings.

Source of air pollution and meteorological data

Original daily data for air pollutant concentrations, including particulate matter ≤ 2.5 μm and ≤ 10 μm and ($PM_{2.5}$ and PM_{10}, respectively), sulfur dioxide (SO_2), carbon monoxide (CO), nitrogen dioxide (NO_2), and ozone (O_3) for each city, were obtained from air quality stations across China from January 2015 to March 2020. For each city, the average concentration for each pollutant before the COVID-19 outbreak (January 2020) was calculated across the entire available period. The data for temperature and precipitation during the coldest and warmest quarter in each city were extracted from WorldClim (Table 1), and the annual mean relative humidity was obtained from the National Meteorological Information Center.

Statistical methods

To quantify the effect of air pollution on COVID-19 risk, we used historical data for air quality between 2015 and 2019 and COVID-19 case reports. Sociodemographic and behavioral confounders were identified in a literature search. We searched PubMed and preprint servers (medRxiv) using the terms "air pollution", "COVID-19", and "SARS-CoV-2", regardless of language and date. Among 74 studies identified, 55 were unrelated to public health. Of the remaining 19 studies, 6 used statistical models to investigate the relationship between air pollution and COVID-19 risk. Three papers involved large-scale and nationwide data from the United States (US), United Kingdom (UK), Italy, Spain, France, and Germany. The association between long-term exposure to air pollutants and COVID-19 risk was assessed using regression with a generalized linear model (GLM):

$$Y_i \sim \text{Poisson}\left(\mu_i, \theta\right) \tag{1}$$

$$\begin{aligned}
&\log(\mu_{it}) = \alpha + \beta_1 Inflow\ from\ Wuhan_i + \beta_2 Peaktime\ of\ inflow_i + \\
&\beta_3 Withincity\ movements_i + \beta_4 GDP_i + \beta_5 Smoking\ prevalence_i + \\
&\beta_5 Secondhand\ smoking\ prevalence\ in\ nonsmokers_i + \\
&\beta_6 Percent\ of\ the\ population\ older\ than\ 65\ years\ old_i + \beta_7 Population_i + \\
&\beta_8 Population\ density_i + \beta_9 Temperature_i + \beta_{10} Rainfall_i + \\
&\beta_{11} Relative\ humidity_i + \beta_{12} Illiteracy\ rate_i + \beta_{13} Hospital\ beds_i + \\
&\beta_{14} PM_{2.5,i} * + \beta_{15} PM_{10,i} * + \beta_{16} SO_{2,i} * + \beta_{17} CO_i * + \beta_{18} NO_{2,i} * + \beta_{19} O_{3,i} *
\end{aligned}$$

(2)

where $Flow_i$ is the passenger volume from Wuhan to city *i* during the Spring Festival 2020, before the Wuhan travel ban; *Peak time of flow* reflects the corresponding peak time. *Within-city movements*$_i$ shows the effect of social distancing within a city between the travel ban and 6 March 2020 in city *i*. GDP is the gross domestic product per capita of city *i*. *Smoking prevalence* and *second-hand smoking prevalence in non-smokers* was extracted from the published literature. The proportion of residents older than 65 years, *illiteracy rate*, *number of hospital beds*, population, and population density of city *i* were extracted from census data. Climate conditions are represented by *temperature* and *rainfall* in summer and winter. The *relative humidity* is the annual mean in city *i*. *Latitude* and *longitude* show the spatial distribution of city *i*. $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3 are the daily average concentration data of air pollutants in city *i* between 1 January 2015 and 31 December 2019. Air pollution variables were included in the model separately because of the high multicollinearity among them. βs are regression coefficients. The variation per unit (VPU) = [exp(variable coefficient) – 1] × 100% was used to describe the effect. The VPU can be interpreted as the percentage increase in the number of COVID-19 cases associated with a 10-μg/m^3 increase in long-term average air pollutant exposure. We used the R software version 3.6.3, MASS package in the analyses (The R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity analysis

We conducted additional sensitivity analyses to assess the robustness of our results. We fit models, omitting adjusted variables separately and air pollutant concentrations in winter and non-winter seasons. To examine the associations after adjusting all other confounders, cities were categorized into three separate groups according to population size: small-sized (0–2.68 million population, n = 98), medium-sized (2.68–4.67 million, n = 97), and large-sized (4.67–30.75 million, n = 98) cities.

Results

Analysis of COVID-19 in China

Between 31 December 2019 and 6 March 2020, a total of 81,132 cases of COVID-19 were reported across China. Of these, 62.6% (50,783/81,132) of cases were clustered in Wuhan city; the remaining 37.4% (30,349/81,132) of cases were distributed across 324 other cities. After 6 March 2020, there were very few locally acquired infections outside Wuhan city during the first wave. There was sustained local transmission of COVID-19 in Wuhan city, so data from that city were not included in the subsequent analysis. Figure 1 shows that the 324 cities had widely distributed COVID-19 cases from 31 December 2019 to 6 March 2020. Additionally, with more travelers from Wuhan before the Spring Festival and more numerous COVID-19 cases reported in each city,

Air pollution reduction and travel restrictions

The average daily concentrations of $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3 during the first wave of the COVID-19 epidemic were 52.13 μg/m^3, 69.58 μg/m^3, 0.93 mg/m^3, 24.58 μg/m^3, and 51.29 μg/m^{3}among the 324 cities, respectively (Supplemental Table 1). On 23 January 2020, China banned travel movement from and to Wuhan, in an attempt to control the epidemic. After that date, a series of social distancing and lockdown policies were implemented throughout China to control the COVID-19 epidemic. During the lockdown period, air pollution emissions were markedly reduced. In particular, average levels of SO_2, $PM_{2.5}$, and PM_{10} were decreased by 21%, 18%, and 16%, respectively, compared with levels before implementation of the restriction policies. NO_2 experienced a reduction of 8.17 $\mu g/m^3$, which was one of the most significant changes among all examined air pollutants after the social distancing measures came into force. The results also indicated that these measures significantly reduced movement within cities during 2020 in comparison with that during 2019 (Figure 2). The air quality in 2020 was also significantly improved, compared with that during the same period in 2019. The changes in average daily concentrations of $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3 were −7.02% ± 32.9%, −19.25% ± 22.03%, −15.06% ± 20.56%, −5.46% ± 18.73%, −20.17% ± 29.56%, and 5.01% ± 16.01%, respectively, from 31 December to 6 March 2020.

Effect of long-term exposure to air pollutants on COVID-19 cases and severe infections

We collected data on a range of confounding variables, such as GDP per capita, smoking prevalence, climate data, illiteracy rate, and age composition (age > 65 years), together with travel movements from Wuhan and within-city movements (as measures of compliance with social distancing). These variables were adjusted in the statistical analysis. The population size of each city and number of COVID-19 deaths and hospital beds were not included in the model because of high multicollinearity with travel movements from Wuhan. The movements of approximately 4.3 billion people during the Spring Festival holiday also induced uncoordinated changes in actual population sizes across cities (Simiao, Juntao et al. 2020). As expected, the number of COVID-19 cases in each city increased with increased population inflow from Wuhan; more infections were reported in cities that had more travelers from Wuhan. Overall, we observed positive and significant associations between confirmed cases of COVID-19 with historical air pollutant concentrations (Figure 1A). In the 324 cities (except Wuhan) that had data on air quality, an increase of 10 $\mu g/m^3$ in the NO_2, $PM_{2.5}$, and PM_{10} concentrations was associated with a 37.8% (95% confidence interval [CI]: 23.8%–52.0%), 32.3% (95% CI: 22.5%–42.4%), and 14.2% (7.9%–20.5%) increase in COVID-19 cases. We also examined the relationship between the number of severe COVID-19 cases and air pollutant levels. An increase of 10 $\mu g/m^3$ in NO_2, $PM_{2.5}$, and PM_{10} concentrations was associated with a 26.3% (95% CI: 11.7%–40.8%), 15.7% (95% CI: 6.3%–25.2%), and 6.43% (95% CI: 0.6%–12.2%) increase in severe COVID-19 cases. The results were statistically significant and robust in sensitivity analyses (Table 2 and Figure 3). The analysis was also carried out using separate datasets. Cities were categorized according to population size into small, medium, and large cities. There was no significant effect of long-term exposure to most of the air pollutants on susceptibility to COVID-19 infection when the data were stratified by population size. While, the effect persisted after stratification in NO_2 and $PM_{2.5}$ on confirmed COVID-19 cases among large cities and small cities, and the impact of PM_{10} in severe COVID-19 cases among large cities. This shows the importance of population as a confounding variable in the analysis.

Discussion

In the present study, we clarified the association between long-term exposure to air pollution and vulnerability to COVID-19 infection during the first epidemic wave in China. The present results were derived from a large, newly compiled and geocoded repository of population and epidemiological data relevant to COVID-19. Indeed, several studies have evaluated the association between air pollution exposure and COVID-19 risk (Copat, Cristaldi et al. 2020). Our finding was in line with studies based on large-scale nationwide data, including from the US (Wu, Nethery et al. 2020), UK (Konstantinoudis, Padellini et al. 2020, Travaglio, Popovic et al. 2020, Travaglio, Yu et al. 2021), Italy (Conticini, Frediani et al. 2020, Fattorini and Regoli 2020), The Netherlands (Andree 2020), Spain, France, and Germany (Ogen 2020), as well as various provinces of China (Yongjian, Jingu et al. 2020). Because the first COVID-19 wave was contained in China, meaning that we were able to investigate the impact of historical air pollution on COVID-19 risk and severity.

In the present study, we found statistically significant evidence that an increase in long-term exposure to NO_2, $PM_{2.5}$, or PM_{10} corresponded to an increase in the number of COVID-19 cases and severe infections. The findings are comparable to the results of previous studies in the US (Wu, Nethery et al. 2020) and Northern Europe (Andree 2020), where levels of $PM_{2.5}$ were also found to be strongly associated with COVID-19 incidence, after adjusting for multiple confounders. However, ours was the first study to use complete data from the first wave of the COVID-19 epidemic in China and to identify the association between long-term exposure to air pollution and COVID-19 risk, after controlling for many meteorological and demographic variables as well as human mobility data. The effects of NO_2 and PM_{10} exposure were also clearly shown in our analysis model, which was a relatively new result. The effects of different components of air pollutants on COVID-19 should be further studied and confirmed.

Our results highlight the importance of air quality improvements with respect to health in China. In an attempt to control the epidemic, on 23 January 2020, non-essential travel was prohibited in and out of Wuhan city, a major transport hub and megacity of 11 million people. Subsequently, the highest level of emergency response was implemented throughout all of China, to reinforce containment of the COVID-19 epidemic. Interventions included the closure of entertainment venues, suspension of within-city public transport, and prohibition of travel to and from other cities in China. These stringent intervention measures significantly reduced air pollution levels in each city during this period (Le, Wang et al. 2020), which was confirmed in our monitoring results (Figure 2). To some extent, the interventions provided an excellent opportunity to examine the benefits of improved air quality (Chen, Wang et al. 2020). Reducing air pollutant concentrations would reduce the incidence of acute respiratory diseases and people’s susceptibility to numerous infectious diseases. Even assuming that problems existed within the multiple interventions, these results were in line with our expectations. Previous studies have demonstrated that exposure to air pollutants is associated with poorer lung function, often measured using forced vital capacity and forced expiratory volume in 1 second (Ackermann-Liebrich U, Leuenberger P et al. 1997, Forbes LJ, Kapetanakis V et al. 2009, Urman R, McConnell R et al. 2014, Adam M, Schikowski T et al. 2015). Exposure to particulate matter may be associated with an increased risk of cardiopulmonary diseases (Chen, Yin et al. 2019), aggravation of the case fatality rate of SARS (caused by SARS-CoV, another strain of coronavirus) (Cui, Zhang et al. 2003), and impaired immune response (Wei and Tang 2018). Oxidant pollutants could also damage the innate immune response and increase host susceptibility to viruses by interfering with the function of macrophages(Karan, Ali et al. 2020, Qu, Li et al. 2020). Nitrogen oxides (NO_X) cause inflammatory responses and worsen pre-existing lung inflammation, resulting in a direct effect on the risk of respiratory diseases (Takahashi Y, Mochitate K et al. 1986, Conticini, Frediani et al. 2020), which is also shown in the Comparative Toxicogenomics Database (http://ctdbase.org). NO_2 is primarily produced by traffic and factories and is less influenced by climatic conditions, so there were reductions in the concentration of NO_X with a decline in within-city movements during the COVID-19 outbreak throughout China. Increased O_3 and SO_2 concentrations were associated with lower COVID-19 risk, which was also consistent with previous studies (Travaglio, Popovic et al. 2020, Yongjian, Jingu et al. 2020). However, the mechanisms underlying the impact of these pollutants on COVID-19 risk remain uncertain.

The association between long-term exposure to air pollution and vulnerability to COVID-19 may be affected by some confounders. We considered many variables for inclusion in the initial model, such as population, inflow from Wuhan, and the number of COVID-19 deaths and hospital beds. However, owing to the collinearity among these four variables, we retained only one of these variables. We believe that in the first COVID-19 wave, the population inflow from Wuhan was the most important factor affecting development of the epidemic. Therefore, only the variable of inflow from Wuhan was retained and the other three were eliminated from the final model. However, we believe that the variable of population is also very important; thus, a hierarchical analysis for the population variable was conducted separately. We found that the association between long-term exposure to air pollutants and vulnerability to COVID-19 differed among different-sized cities. In large-sized cities, the association was more obvious, which may be owing to better health care, better case reporting, and better testing policies in large cities. Therefore, the effect of population size is complex and needs further analysis.

As with other novel infectious diseases, there were many challenges in the diagnosis of COVID-19 during the first epidemic wave (Arons, Hatfield et al. 2020, Li, Geng et al. 2020). Concern has been expressed about the sensitivity and specificity of the tests initially used to identify people infected with SARS-CoV-2. The performance of the detection methods has improved over time (Carter, Garner et al. 2020). At the same time, there is a lack of adequate testing in most countries, and treatment of patients with COVID-19 in many jurisdictions is inadequate owing to overburdened health systems. As a result, many cases and deaths that were attributable to COVID-19 have not been confirmed. These issues may have some influence on the findings of this study. For example, this situation would lead to inaccuracies in the number of confirmed cases or severe cases of COVID-19 infection, which would cause some bias in the results. This may also be a reason that rates of greater severity of the disease are consistently lower. However, early studies during the epidemic can draw on the results of a pure transmission model. The present study focused on the association between air pollution and COVID-19 in the first wave in Wuhan, China. The variables included important human mobility data, such as inflow from Wuhan and peak time of inflow from Wuhan. These data would well reflect some important scientific problems in the early stages of an outbreak of a new infectious disease.

Several important caveats are worth mentioning. First, the data included here were all from mainland China; it is therefore unclear whether the findings can be generalized to other countries without data on historic air pollution exposure. Second, there are currently no high-quality records at city level regarding severe COVID-19 infections and ICU admissions, although we have attempted to fill this gap by using province-level reports. Third, air pollution data from ambient air quality stations across China do not necessarily reflect exposure to indoor air pollution; this may therefore bias the results. Finally, we do not know the exact number of cases because we do not know the number of asymptomatic and mildly symptomatic cases that may not have been recorded. These data will not be available until there has been a systematic survey of infection (e.g., via serological testing) across China. However, we reported a national-level disease pattern covering 324 cities and its potential association with long-term exposure to air pollutants.

Conclusions

In the present study, we found a significant positive association between long-term exposure levels to $PM_{2.5}$, PM_{10}, NO_2, and the risk and severity of COVID-19 infection in China. Our findings suggest that air pollution may be related to population vulnerability to COVID-19. Interventions to control the COVID-19 outbreak in China successfully reduced air pollution levels and potentially prevented further cases of acute respiratory disease. Improved air quality may be conducive to reducing the hazards of respiratory infectious diseases. The link between COVID-19 and air pollution deserves more definitive and global data analysis.

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The authors declare that they have no known competing financial interest or personal relationships that could have influenced the work reported in this paper.

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Table 1. Databases and sources of coronavirus disease 2019 (COVID-19) and air pollution data

Database	data provider	Source
COVID-19		
Confirmed COVID-19 cases	Provincial Health Committees which contained data of each city	Official website of health commission of 34 provincial-level administrative units and 342 city-level units
Severe COVID-19 cases	Provincial Health Committees which contained data of each city	Official website Health commission of 34 provincial-level
COVID-19 deaths	Provincial Health Committees which contained data of each city	Official website of health commission of 34 provincial-level administrative units and 342 city-level units
Human mobility data		
Outflow from Wuhan	Baidu location-based services mobile phone data provided by the telecommunications operators	https://qianxi.baidu.com/
Within-city movements	The activities index of human mobility with a city	https://qianxi.baidu.com/
Meteorological data		
$PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3	China National Environmental Monitoring Centre,2015-2019	http://www.cnemc.cn/
Temperature	Mean Temperature of Warmest/Coldest Quarter (2015-2019)	https://www.worldclim.org/data/bioclim.html
Rainfall	Precipitation of Warmest/Coldest Quarter (2015-2019)	https://www.worldclim.org/data/bioclim.html
Relative Humidity	National Meteorological Information Center (CMA Meteorological Data Center, 2015-2019)	http://data.cma.cn/
Demographic data		
Gross domestic product (GDP)	China City Statistical Yearbook 2019	http://www.stats.gov.cn/tjsj/ndsj/2019/indexeh.htm
Age structure	Sixth National Population Census of the People's Republic of China (2013)	http://www.stats.gov.cn/tjsj/pcsj/rkpc/6rp/indexch.htm
Smoking and second-hand smoking prevalence	Chinese National Nutrition and Health Survey (NNHS)	PMID: 24698853
Hospital beds	China City Statistical Yearbook 2019	http://www.stats.gov.cn/tjsj/ndsj/2019/indexeh.htm
Illiteracy rate	Sixth National Population Census of the People's Republic of China (2013)	http://www.stats.gov.cn/tjsj/pcsj/rkpc/6rp/indexch.htm

COVID-19, coronavirus disease 2019; $PM_{2.5}$, particulate matter ≤ 2.5 μm; PM_{10}, particulate matter ≤ 10 μm; SO_2, sulfur dioxide; CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; CMA, China Meteorological Administration.

Table 2. Impact of historical air pollution exposure on cases of COVID-19

Covariates	**Confirmed COVID-19 cases**			**Severe COVID-19 cases**		
	Coefficient (95%CI)	std	P	Coefficient (95%CI)	std	P
NO_2	0.378（0.238,0.52）	0.072	<0.001	0.263(0.117,0.408)	0.074	<0.001
Intercept	-1.697（-3.436,0.021）	0.882	0.055	-1.919(-3.437,-0.401)	0.771	0.013
Inflow from Wuhan	0.007（0.007,0.008）	<0.001	<0.001	0.016(0.013,0.019)	0.002	<0.001
Within-city movements	-1.14（-1.382,-0.901）	0.123	<0.001	-0.853(-1.098,-0.609)	0.124	<0.001
Peak of inflow from Wuhan	0.175（0.133,0.218）	0.022	<0.001	0.086(0.043,0.13)	0.022	<0.001
Mean temperature of coldest quarter	-0.023（-0.045,-0.001）	0.011	0.040	0.006(-0.014,0.027)	0.010	0.528
Relatively humidity	0.048（0.029,0.067）	0.010	<0.001	0.028(0.012,0.045)	0.008	0.001
Illiteracy rate	0.053（0.014,0.09）	0.019	<0.001	0.0188(-0.017,0.055)	0.018	0.305
$PM_{2.5}$	0.323（0.225,0.424）	0.051	<0.001	0.157(0.063,0.252)	0.048	0.001
Intercept	-1.237（-2.841,0.329）	0.809	0.128	-1.313(-2.689,0.062)	0.699	0.061
Inflow from Wuhan	0.007（0.006,0.007）	<0.001	<0.001	0.015(0.012,0.018)	0.002	<0.001
Within-city movements	-1.376（-1.617,-1.139）	0.122	<0.001	-0.961(-1.192,-0.731)	0.117	<0.001
Peak of inflow from Wuhan	0.137（0.096,0.179）	0.021	<0.001	0.077(0.033,0.121)	0.022	0.001
Mean temperature of coldest quarter	-0.003（-0.027,0.022）	0.012	0.790	0.01(-0.01,0.03)	0.010	0.329
Relatively humidity	0.052（0.032,0.071）	0.010	<0.001	0.026(0.01,0.042)	0.008	0.002
Illiteracy rate	0.049（0.008,0.087）	0.020	0.016	0.019(-0.017,0.056)	0.018	0.293
PM_{10}	0.142（0.079,0.205）	0.032	<0.001	0.0643(0.006,0.122)	0.032	<0.001
Intercept	-1.183（-3.023,0.609）	0.927	0.203	-1.183(-2.861,0.217)	0.927	0.203

Inflow from Wuhan	0.007（0.006,0.007）	<0.001	<0.001	0.007(0.012,0.018)	<0.001	<0.001
Within-city movements	-1.346（-1.604,-1.092）	0.131	<0.001	-1.346(-1.208,-0.742)	0.131	<0.001
Peak of inflow from Wuhan	0.148（0.104,0.194）	0.023	<0.001	0.148(0.037,0.126)	0.023	<0.001
Mean temperature of coldest quarter	-0.009（-0.033,0.016）	0.013	0.455	-0.009(-0.011,0.03)	0.013	0.455
Relatively humidity	0.054（0.032,0.076）	0.011	<0.001	0.054(0.012,0.046)	0.011	<0.001
Illiteracy rate	0.046（0.003,0.086）	0.021	0.033	0.046(-0.021,0.053)	0.021	0.033

COVID-19, coronavirus disease 2019; $PM_{2.5}$, particulate matter ≤ 2.5 μm; PM_{10}, particulate matter ≤ 10 μm; NO_2, nitrogen dioxide; CI, confidence interval.

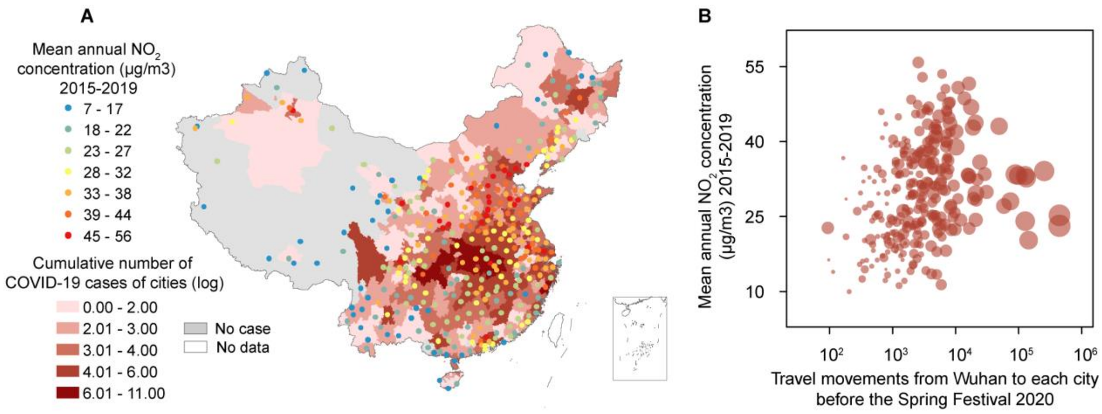


Figure 1. Air pollution exposure, coronavirus disease 2019 (COVID-19) cases, and travel movements in 324 cities of China during Spring Festival 2020. (A) Distribution of cities with data on nitrogen dioxide (NO_2) concentrations and COVID-19 cases. Shading from light red to dark red represents cumulative number of confirmed COVID-19 cases in each city, from low to high, respectively, from 31 December 2019 to 6 March 2020; white area represents no data, and grey area represents no cases. Points colored from blue to red represent historic mean annual NO_2 concentrations (μg/m^3), from low to high, respectively, during January 2015 and December 2019, prior to the COVID-19 epidemic. (B) Association between the cumulative number of confirmed cases, the number of human movements from Wuhan to each city, and historic mean annual NO_2 concentration. The area of the circles represents the cumulative number of cases reported by 6 March 2020.

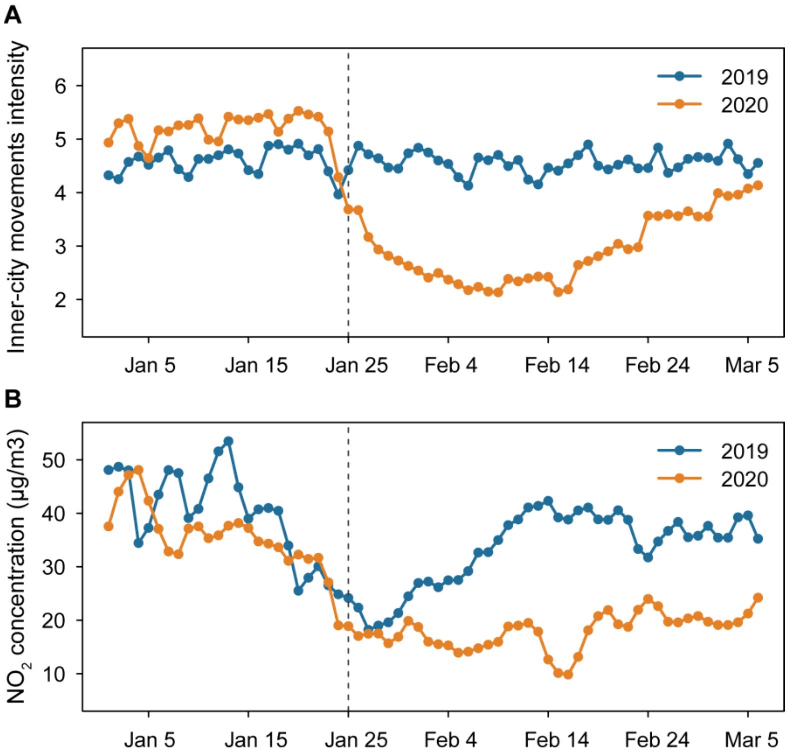


Figure 2. (A) Average within-city movement intensity and (B) air pollutant concentration in 324 cities of China during the 2020 COVID-19 outbreak (orange line), compared with the same period in 2019 (blue line).

NO_2, nitrogen dioxide.

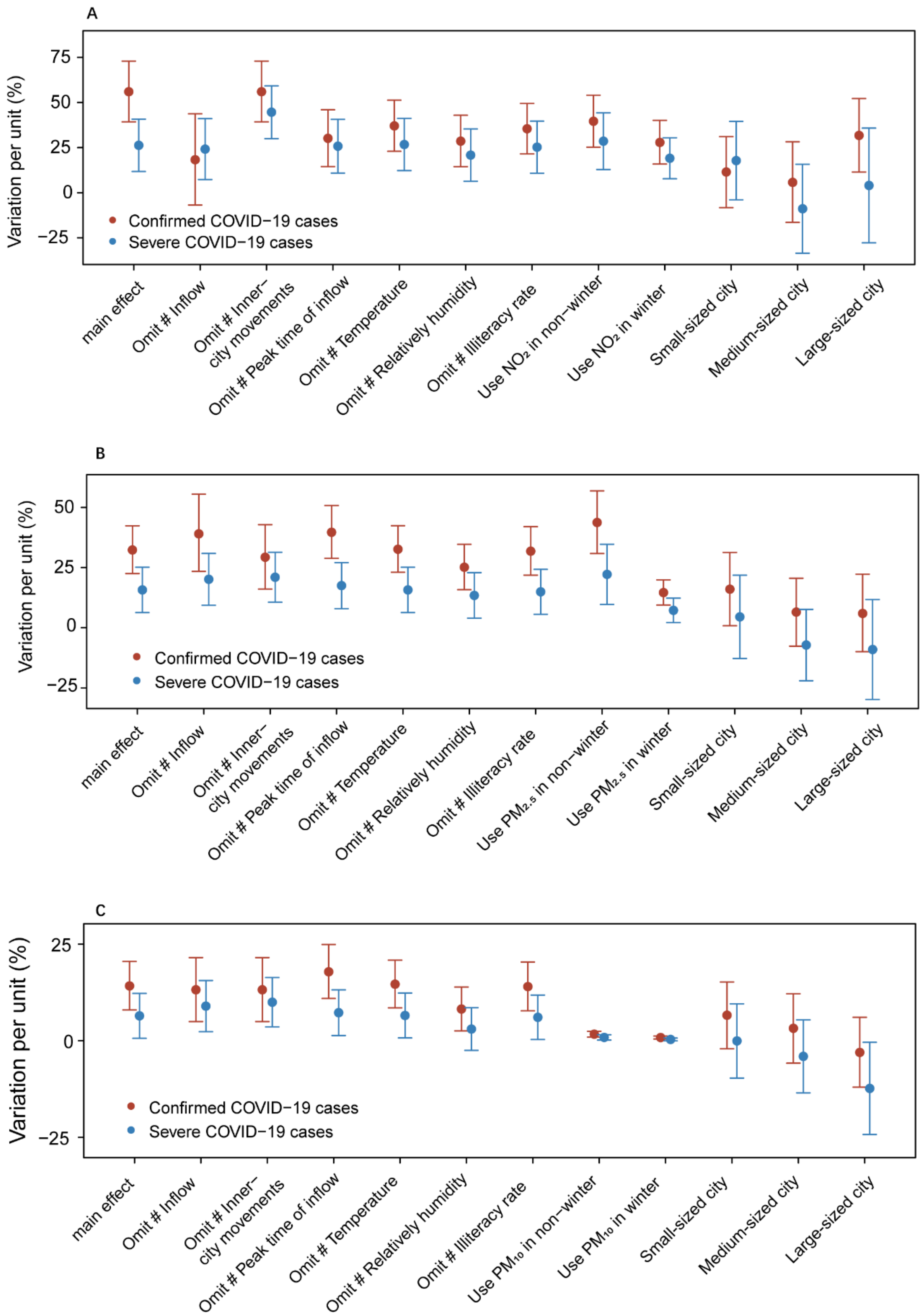

A
Variation per unit (%)
75
50
25
0
−25
Confirmed COVID−19 cases
Severe COVID−19 cases
main effect
Omit # Inflow
Omit # Inner−city movements
Omit # Peak time of inflow
Omit # Temperature
Omit # Relatively humidity
Omit # Illiteracy rate
Use NO₂ in non−winter
Use NO₂ in winter
Small-sized city
Medium-sized city
Large-sized city
B
Variation per unit (%)
50
25
0
−25
Confirmed COVID−19 cases
Severe COVID−19 cases
main effect
Omit # Inflow
Omit # Inner−city movements
Omit # Peak time of inflow
Omit # Temperature
Omit # Relatively humidity
Omit # Illiteracy rate
Use PM2.5 in non−winter
Use PM2.5 in winter
Small-sized city
Medium-sized city
Large-sized city
C
Variation per unit (%)
25
0
−25
Confirmed COVID−19 cases
Severe COVID−19 cases
main effect
Omit # Inflow
Omit # Inner−city movements
Omit # Peak time of inflow
Omit # Temperature
Omit # Relatively humidity
Omit # Illiteracy rate
Use PM10 in non−winter
Use PM10 in winter
Small-sized city
Medium-sized city
Large-sized city

Figure 3. Variation per unit and 95% confidence intervals, (A) NO_2, (B) $PM_{2.5}$, and (C) PM_{10}. The variation per unit (VPU) = [exp(variable coefficient) – 1] × 100%. The VPU can be interpreted as the percentage increase in the number of COVID-19 cases associated with a 10-μg/m^3 increase in long-term average NO_2 and $PM_{2.5}$. The VPU from the main analysis was adjusted for confounding factors. In the sensitivity analyses, we omitted each confounding factor separately, and used seasonal air pollutant concentrations.

COVID-19, coronavirus disease 2019; $PM_{2.5}$, particulate matter ≤ 2.5 µm; PM_{10}, particulate matter ≤ 10 µm; NO_2, nitrogen dioxide.

Figure1

Click here to access/download;Figure;figure1.tif

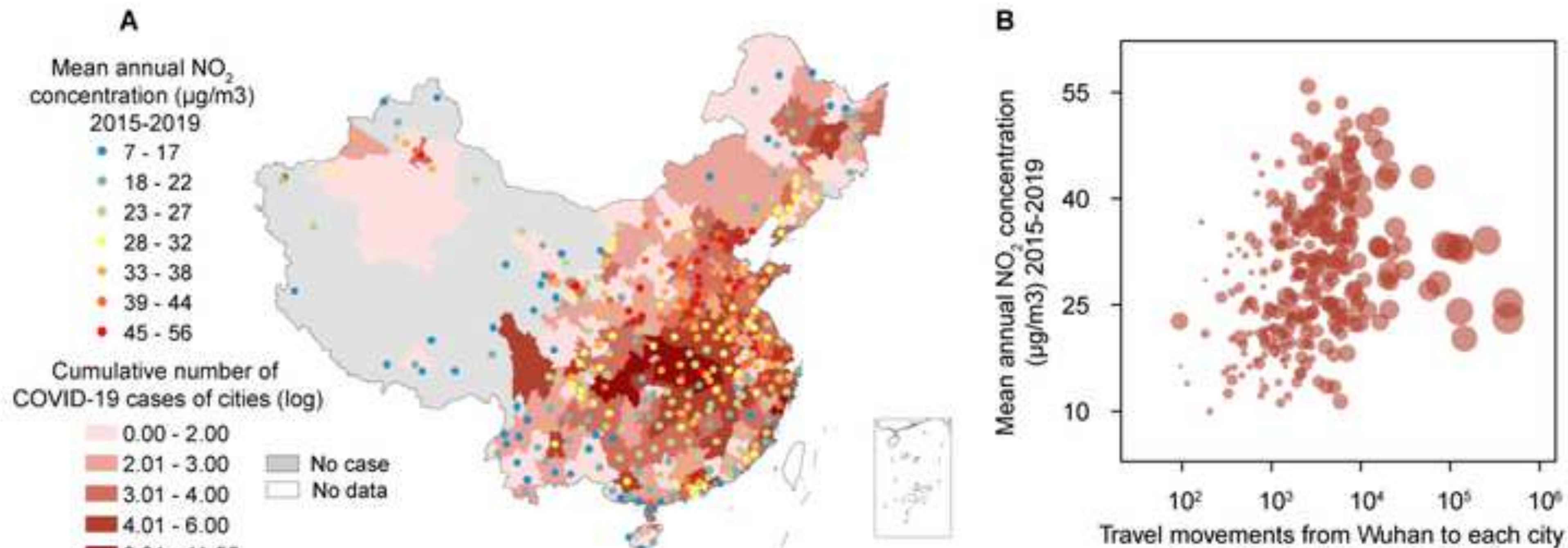


Figure2

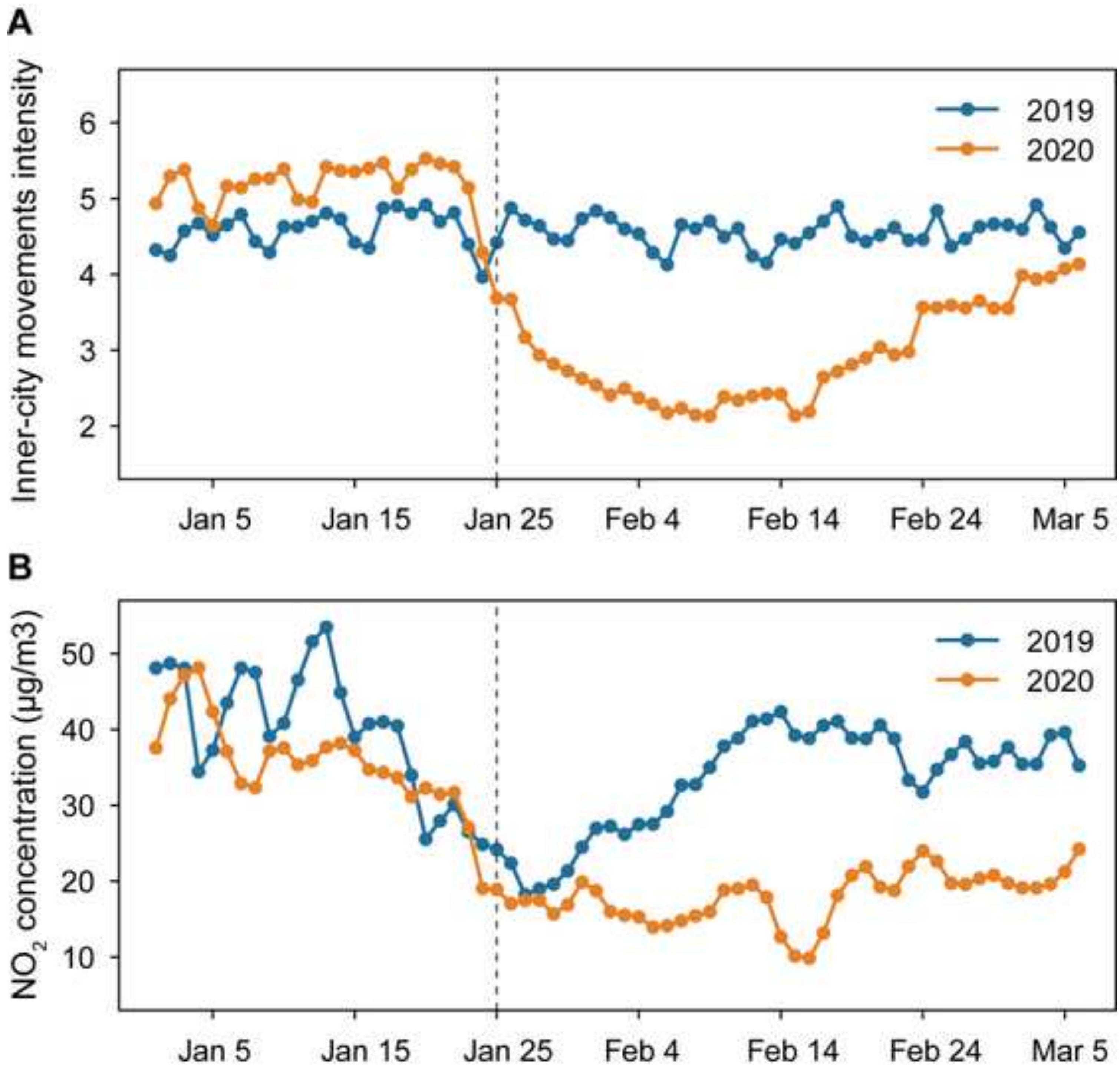
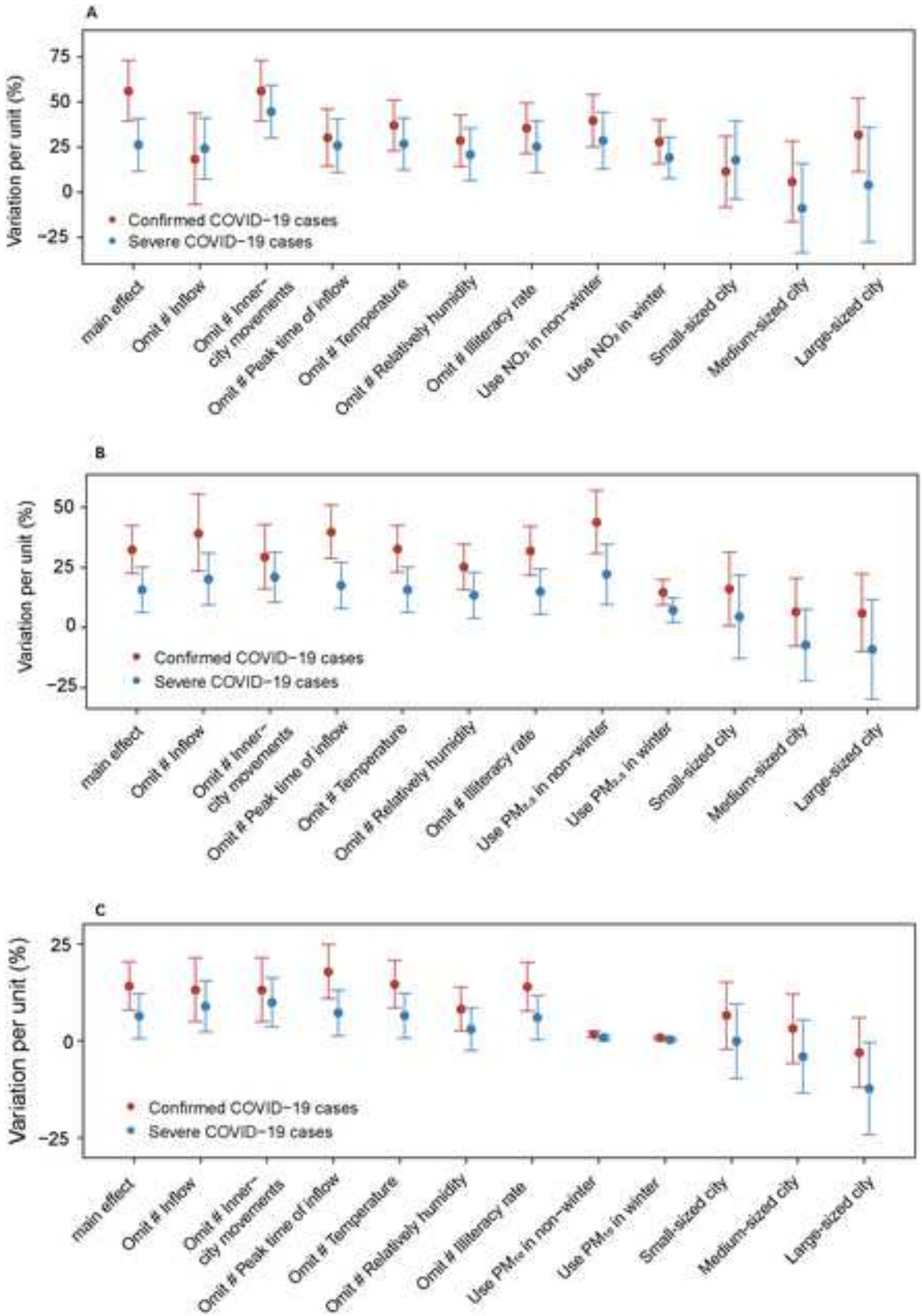

A
Inner-city movements intensity
6
5
4
3
2
Jan 5
Jan 15
Jan 25
Feb 4
Feb 14
Feb 24
Mar 5
2019
2020
B
NO_2 concentration (μg/m3)
50
40
30
20
10
Jan 5
Jan 15
Jan 25
Feb 4
Feb 14
Feb 24
Mar 5
2019
2020

Figure3


A
Variation per unit (%)
Confirmed COVID−19 cases
Severe COVID−19 cases
main effect
Omit # Inflow
Omit # Inner−city movements
Omit # Peak time of inflow
Omit # Temperature
Omit # Relatively humidity
Omit # Illiteracy rate
Use NO₂ in non−winter
Use NO₂ in winter
Small-sized city
Medium-sized city
Large-sized city
B
Use PM₂.₅ in non−winter
Use PM₂.₅ in winter
C
Use PM₁₀ in non−winter
Use PM₁₀ in winter

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Author contributions: P.Z., H.T., G.J. and N.C.S. designed the study. H.S. collected and processed the LBS data. Y. L., X.Y., and B. L. collected the statistical data. Y.L. and C.-H.W. conducted the analyses. Z.C. H.T., C.-H.W., M.U.G.K. and Y.Z. edited the manuscript. P.Z. and Z.C. wrote and revised the manuscript. All authors read and approved the manuscript.

A~~The a~~ssociation between coronavirus disease 2019 (COVID-19) and long-term exposure to air pollution: evidence from the first epidemic wave in China

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Abstract

People with chronic obstructive pulmonary disease, cardiovascular disease, or hypertension have a high risk of developing severe coronavirus disease 2019 (COVID-19) and of COVID-19 mortality. However, the association between long-term exposure to air pollutants, which ~~would~~ increases cardiopulmonary damage, and vulnerability to COVID-19 has not yet been fully established. We collec~~a~~ted data of confirmed COVID-19 cases during the first wave of the epidemic in mainland China. We fitted a generalized linear model using city-level COVID-19 cases and severe cases as the outcome, and long-term average ~~levels of~~ air pollutant levels~~s~~ as the exposure. Our analysis was adjusted using several variables, including a mobile phone dataset, covering human movement from Wuhan before the travel ban and movements within each city during the ~~time~~ period of the emergency response. Other variables included ~~census,~~ smoking prevalence, climate data, ~~and~~ socio-economic data, education level, ~~–~~ and number of hospital beds ~~data from~~for 324 cities in China. After ~~We~~ adjusting~~ed~~ for human mobility and socio-economic factors~~,~~, we ~~–and~~ found ~~that~~ an increase of 37.8% (95% confidence interval [CI]: 23.8%–52.0%), 32.3% (95% CI: 22.5%–42.4%), and 14.2% (7.9%–20.5%) ~~increase~~ in the number of COVID-19 cases for every 10-μg/m^3 increase in ~~the~~ long-term exposure to NO_2, $PM_{2.5}$ ~~a~~, and PM_{10} ~~r~~, respectively. However, when stratifying the data ~~by~~according to population size~~-classes~~, the association became non-~~in~~significant~~the association varied in different population sized cities~~. The present results are derived from a large, newly compiled and geocoded repository of population and epidemiological data relevant to COVID-19. The findings suggested that air pollution may be related to ~~the~~ population vulnerability to COVID-19 infection, although the extent to which this relationship is confounded by city population density needs further exploration~~. The link between COVID-19 and air pollution deserves a more definitive and global data analysis~~.

Main Finding

This research reported a national-level association with long-term exposure to air pollutants and COVID-19 cases covering 324 cities in China.

Key words

Coronavirus disease 2019; COVID-19; Air pollution; Chronic exposure~~Long-term exposure~~

Introduction

C~~The novel c~~oronavirus disease 2019 (COVID-19) has rapidly spread across the world. To date, ~~,~~ ~~and~~ the virus that causes COVID-19, severe acute respiratory disease coronavirus 2 (SARS-CoV-2), ~~so far had~~has infected more than ~~63~~ 101 million people and led to ~~, with~~ approximately ~~1.5~~2.16 million fatalities, according to John Hopkins University. Currently, several reports suggest~~ed~~ that air pollution is associated with an increased~~the~~ risk of death or severe ~~cases~~ illness among ~~the population~~people with ~~infected~~ COVID-19 infection (Magazzino, Mele et al. 2020, Wu, Nethery et al. 2020, Yao, Pan et al. 2020, Travaglio, Yu et al. 2021), ~~based~~ on the basis of ~~the~~ a biologically plausible pathway that ~~which~~ might lead to serious deterioration (Conticini, Frediani et al. 2020, Frontera, Cianfanelli et al. 2020). ~~The virus (~~SARS-CoV-2~~)~~ can induce~~s~~ respiratory disstress, so individuals with a compromised respiratory system are expected to be more vulnerable to infection (Qu, Li et al. 2020), and people with pre-existing conditions are more vulnerable to severe infection. A ~~M~~meta-analysis ~~has~~ showed~~n~~ that chronic obstructive pulmonary disease (COPD), cardiovascular disease ~~(CVD)~~, and hypertension are associated with severe COVID-19 infection and admission to the intensive care unit~~s~~ (ICU~~s~~) (Jain and Yuan 2020).

Long-term exposure to air pollution affects lung function and is associated with the risk of many lung diseases~~impacts~~, including ~~the~~ an increased prevalence of COPD, acute lower respiratory illness, and lung cancer (Götschi, Heinrich et al. 2008, Lelieveld, Evans et al. 2015, Doiron, de Hoogh et al. 2019, Liu, Chen et al. 2019). Moreover, recent ~~implementation tried~~research has put forth ~~to explain the~~ potential biological mechanisms of alveolar angiotensin-converting enzyme 2 (~~(~~ACE-2)~~)~~ and population susceptibility ~~on~~ to COVID-19 infection (Paital and Agrawal 2020). A~~In a~~dditionally, chronic lung exposure to pollutants may lead to injury ~~due~~ owing to pulmonary damage ~~by~~ from oxidative stress, macrophage disfunction, and a disrupted epithelial barrier ~~could facilitate the access of inhaled pathogens~~, thereby increasing~~us~~ ~~enhancing~~ susceptibility of the upper airways (Ciencewicki and Jaspers 2007, Frontera, Cianfanelli et al. 2020, Zhu, Xie et al. 2020). This~~at~~ implies ~~d~~ that long-term exposure might increase ~~the~~ vulnerability to lung diseases, thereby~~us~~ affecting the risk of COVID-19 infection ~~risk~~ in the whole population. However, recent studies t~~r~~end to ignore the broad implications of long-term ~~impairs~~ effects on the lungs. Furthermore, few studies have considered the important role of human travel and movement in the ~~progress of COVID-19~~ spatial spread of COVID-19, which might serve as a critical confounding variable in evaluating the effects of ~~caused by~~ air pollution. We ~~need to~~must understand the impact of air pollution exposure on COVID-19 infection and disease severity (Villeneuve and Goldberg 2020) in the general public~~and to the public~~, to ~~. This could~~ ~~will~~ help ~~to~~ improve future model~~l~~ing and disease burden calculations in countries around the world.

During the first epidemic wave of COVID-19 in China, to prevent further dissemination of the ~~illness~~disease, officials in Wuhan prohibited all transport in and out of the city on 23 January 2020. In the following days, cities across mainland China ~~activated~~ launched the highest level ~~of~~ emergency response and were able to ~~contained~~ control ~~led~~ the epidemic~~outbreaks~~ outside of Wuhan ~~up until~~by 6 March 2020. These measures substantially reduced air pollution~~:~~, ~~which~~ ~~was~~as confirmed by a significant reduction in pollution levels ~~was~~ observed across cities in China between January and March 2020 (Chen, Wang et al. 2020, Villeneuve and Goldberg 2020). These d~~D~~ata ~~on~~from Chinese cities (excluding Wuhan) ~~are~~ were ideal to assess the relationship between long-term average air pollution exposure and COVID-19 risk ~~(Figure 1)~~ because these cities had widely distributed COVID-19 cases~~, –~~ and highly variable historical air quality~~, and~~, which had~~ve~~ been ~~surveyed~~ comprehensively surveyed under consistent criteria and data standards across the country. Air pollution ~~has~~ produces both acute and long-term health effects, so a reduction in air pollution ~~reduction~~ levels can serve~~s~~ as a natural experiment ~~to~~ in how to offset ~~– the~~ potential acute effects of air pollution~~in particular~~.

Considering the proven link between air pollution and the high risk of severe COVID-19 ~~severity~~infection, we ~~therefore~~ suspected that long-term exposure to air pollutants, which increases cardiopulmonary damage, would be associated with increased vulnerability to COVID-19. To test this hypothesis, we identified socio-demographic and behavio~~u~~ral confounders ~~were identified~~ through a literature search. We first investigated the effect of travel and movement ~~s~~ from Wuhan city, the location where COVID-19 was first recorded~~,~~ and from where it spread across China. D ~~In 2020, d~~uring ~~travel for~~ the Spring Festival holiday in 2020, approximately 4.3 million people travel~~l~~ed ~~out of~~from Wuhan to other cities in China (Tian, Liu et al. 2020). These~~is~~ travel patterns were~~is~~ strongly associated with the total number of cases reported ~~from~~ in each city, suggesting that the outbreaks across China were mainly seeded ~~from~~ in Wuhan city.

~~2.~~Methods

~~2.1~~ Epidemiological and demographic data

We collected epidemiological data from ~~the~~ official reports of the health commissions of 324 cities, excluding Wuhan (Table 1). These included daily reports from 31 December 2019 to 6 March 2020, but excluded newly-reported, locally-acquired infections. Data on the ~~percentage~~ proportion of severe COVID-19 cases were obtained from official reports of Provincial Health Committees and ~~were~~ used to interpolate the city-level values. The National Health Commission of the People's Republic of China defined uniform diagnosis and treatment criteria of "2019 ~~novel~~ novel ~~coronavirus~~ coronavirus pneumonia", to measure the number of outbreaks~~,~~. T~~t~~he reporting system was supported by local health-related departments, including hospitals and Centers for Diseases Control and Prevention (CDCs) at the provincial or county level (Zanin, Xiao et al. 2020). In the first wave of the COVID-19 epidemic, these local CDCs ~~tried~~ sought to detect the largest possible number of infections, but people ~~who had~~with a fever and a travel history to Wuhan ~~set~~ were the priority groups for~~to~~ testing. Socio-economic data, including the gross domestic product (GDP) per capita and number of hospital beds, were obtained from the China City Statistical Yearbook 2019. The age structure and illiteracy rate of people aged 15 years and older ~~for~~ in each city were obtained from the Sixth National Population Census of the People's Republic of China, which was conducted by the National Bureau of Statistics of People's Republic of China in 2013. The prevalence of s~~S~~moking ~~prevalence~~ and second-hand smoking ~~prevalence~~ ~~in~~among non-smokers ~~were~~ was obtained from the Chinese National Nutrition and Health Survey ~~(NNHS)~~ (Wu, Huxley et al. 2008, Xia, Zheng et al. 2019). These were ecological ~~data were ecological~~ and not individual data, which did not involve personal ~~privacy~~ information; therefore, an ethics review was not required.~~, so there should be no ethical issue.~~

~~2.2~~ *Human m~~M~~obility d~~D~~ata*

Human movements were tracked using mobile phone data from Baidu location-based services ~~(LBS)~~ and telecommunications operators (Table 1). The number of recorded movements from Wuhan ~~city~~ to other cities across China was calculated from 11 to 23 January 2020. On 23 January, movements from Wuhan dropped to nearly ~~reached almost~~ zero because of the travel ban. M~~Travel m~~ovements within each city were recorded daily until 6 March. The within-city movement index was extracted from the same operators and was measured, to reflect the average times people ~~went out~~traveled from their location inside ~~the~~ each city every day. This database was ~~implemented~~ developed to describe people's ~~response to~~ compliance with physical distancing~~e~~ policies~~ties~~, ~~such as~~which included suspending intra-city public transport, closing entertainment venues, and banning public gatherings.

~~2.3~~S ~~Data s~~ource of a~~for A~~ir p~~P~~ollution and m~~M~~eteorological data

Original daily data for ~~particulate matter~~air pollutant~~s~~ concentrations, including particulate matter ≤ 2.5 μm and ≤ 10 μm and ($PM_{2.5}$~~,~~ and ~~–~~PM_{10}, respectively), sulfur dioxide (SO_2), carbon monoxide (~~,~~CO), nitrogen dioxide (NO_2),~~,~~ and ozone (O_3) ~~–~~for each city, were obtained from air quality stations across China from January 2015 to March 2020. For each city, the average concentration for each pollutant before the COVID-19 outbreak (January 2020) was calculated across the ~~whole~~ entire available period~~ available~~. The data for temperature and precipitation ~~of~~ during the coldest and warmest quarter in each city ~~was~~ were extracted from WorldClim (Table 1), and the annual mean relative humidity was obtained from the National Meteorological Information Center.

~~2.4~~ *Statistical m~~M~~ethods*

To quantify the effect of air pollution on COVID-19 risk, we used ~~the~~ historical data for air quality between 2015 and 2019 and COVID-19 case reports. Socio-demographic and behavio~~u~~ral confounders were identified ~~through~~ in ~~the~~ a literature search. We searched PubMed and preprint servers (medRxiv) using the terms "air pollution", "COVID-19", ~~–~~and "SARS-CoV-2", regardless of language and date. Among 74 studies identified, 55 were ~~of the 74 results were~~ unrelated to public health. Of the remaining 19 studies, ~~.~~6 ~~studies of the remaining 19 studies~~ used statistical models to investigate the relationship between air pollution and COVID-19 risk. Three papers involved large-~~-~~scale and nationwide data ~~in~~ from the United States (US), United Kingdom (UK), Italy, Spain, France, and Germany. The association between long-term exposure to air pollutants and COVID-19 risk was assessed ~~by~~ using regression with a generalized linear model (GLM):

$$Y_i \sim \text{Poisson}(\mu_i, \theta) \quad (1)$$

$$\log(\mu_{it}) = \alpha + \beta_1 Inflow\ from\ Wuhan_i + \beta_2 Peaktime\ of\ inflow_i + \beta_3 Withincity\ movements_i + \beta_4 GDP_i + \beta_5 Smoking\ prevalence_i + \beta_5 Secondhand\ smoking\ prevalence\ in\ nonsmokers_i + \beta_6 Percent\ of\ the\ population\ older\ than\ 65\ years\ old_i + \beta_7 Population_i + \beta_8 Population\ density_i + \beta_9 Temperature_i + \beta_{10} Rainfall_i + \beta_{11} Relative\ humidity_i + \beta_{12} Illiteracy\ rate_i + \beta_{13} Hospital\ beds_i + \beta_{14} PM_{2.5,i} * + \beta_{15} PM_{10,i} * + \beta_{16} SO_{2,i} * + \beta_{17} CO_i * + \beta_{18} NO_{2,i} * + \beta_{19} O_{3,i} * \tag{2}$$

where $Flow_i$ is the passenger volume from Wuhan to city *i* during the Spring Festival 2020, before the Wuhan travel ban;~~,~~ ~~and~~ *Peak time of flow* reflects the corresponding peak time. *Within-city movements*$_i$ shows the effect of social distancing within a city between the travel ban and 6 March 2020 ~~of~~ in city *i*. GDP is the gross domestic product per capita of city *i*. *Smoking prevalence* and *second-hand smoking prevalence in non-smokers* was extracted from the published ~~article~~literature. The proportion of residents older than 65 years, *illiteracy rate*, *number of hospital beds*, population, and population density of city *i* were extracted from census data. Climate conditions ~~were~~ are ~~shown~~ represented by *temperature* and *rainfall* in summer and winter. The *relative humidity* ~~was~~ is the annual mean ~~of the year of~~in city *i*. *Latitude* and *longitude* show the spatial distribution of city *i*. $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3 ~~show~~ are the daily average concentration data of air pollutants ~~of~~ in city *i* between 1 January 2015 and 31 December 2019. Air pollution variables were included in the model separately because of the high multicollinearity among them. βs are regression coefficients. The variation per unit (VPU) = [exp(variable coefficient) – 1] × 100% was used to describe the effect. The VPU can be interpreted as the percentage increase in the number of COVID-19 cases associated with a 10~~-~~ μg/m^3 ~~-~~increase in long-term average air pollutant~~s~~ exposure. ~~The analysis~~We used the R software ~~(R Foundation for Statistical Computing,~~ version 3.6.3~~)~~, MASS package in the analyses (The R Foundation for Statistical Computing, Vienna, Austria).

~~2.5~~ *Sensitivity a~~A~~nalysis*

We conducted a~~A~~dditional sensitivity analyses to assess the robustness of our results ~~were conducted~~. We fit models, omitting adjusted variables separately and air pollutant~~s~~ concentrations in winter and non-winter seasons. To examine the associations after adjusting all other confounders, c~~C~~ities were categorized ~~by population size~~ into three separate groups according to population size: ~~,~~ small-sized (0–2.68 million population, n = 98), medium-sized (2.68–4.67 million, n = 97), and large-sized (4.67–30.75 million, n = 98) cities.~~) to examine the association after adjusting all other confounders.~~

~~3.~~Results

~~3.1~~ *Analysis of COVID-19 in China*

Between 31 December 2019 and 6 March 2020, a total of 81,132 cases of COVID-19 were reported across China. Of these, 62.6% (50,783/81,132) of cases were clustered in Wuhan city; ~~,~~ ~~and~~ the remaining 37.4% (30,349/81,132) of cases were distributed across 324 other cities. After 6 March 2020, there were very few locally-acquired infections outside Wuhan city ~~in~~ during the first wave. There was sustained local transmission of COVID-19 in Wuhan city, so data from ~~there~~ that city were not included in the subsequent analysis. Figure 1 shows that the 324~~n~~ cities had widely distributed ~~with~~ COVID-19 cases ~~across the countries~~ from 31 December 2019 to 6 March 2020. Additionally, ~~historical air quality from 2015 to -2019 is was associated with travel movement from Wuhan,~~ also and ~~the~~with more travelers from Wuhan before the Spring Festival ~~the~~ and more numerous COVID-19 ~~infection~~ cases reported in each city,

~~3.2~~ *Air pollution reduction and travel restrictions*

The average daily concentrations of $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2 ~~O_3~~ ~~a~~, and ~~CO~~ O_3 during the first wave of the COVID-19 epidemic were 52.13 μg/m^3, 69.58 μg/m^3, ~~24.58~~0.93 ~~μ~~mg/m^3, ~~11.86~~24.58 μg/m^3, and 51.29 μg/m^3~~, and 0.93 mg/m^3~~ among the 324~~se~~ cities, respectively (Supplemental Table 1). On 23 January 2020, China banned travel movement from and to Wuhan, in an attempt to ~~contain~~ control the epidemic. ~~Since then~~After that date, a series of social distancing and lockdown policies were implemented throughout ~~cy in the whole~~ China ~~has had implemented~~ to ~~reinforce~~ control the ~~pandemic of~~ COVID-19 epidemic. During the lockdown period, ~~the~~ air pollution emissions were ~~was~~ markedly reduced. In particular, ~~, especially the~~ average levels of SO_2, $PM_{2.5}$, and PM_{10} were decreased by 21%, 18%, and 16%, respectively, compared with ~~those~~levels ~~the average level~~ before implementation of the restriction policies. NO_2 experienced a reduction of 8.17 μg/m^3, which ~~is~~ was one of the most significant~~ly~~ changes among all examined air~~d~~ pollutants after the ~~conducting these~~ social distancing measures came into force. T~~In addition, our t~~he results also indicated that these measures ~~have~~ had significantly reduced ~~the~~ movement within cities ~~in~~during 2020 in comparison~~ed~~ with that ~~in~~during 2019 (Figure 2). The ~~average~~ air quality in 2020 was also significantly improved, compared with that during the same period in 2019. The changes in average daily concentrations of $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3 were −7.02% ± ~~±~~32.9%, −19.25% ± 22.03%, −15.06% ± 20.56%, −5.46% ± 18.73%, −20.17% ± 29.56%, and 5.01% ± 16.01%, respectively, from 31 December to 6 March 2020.

Effect of l~~3.3 L~~ong-term exposure to air pollutants on COVID-19 cases and severe infections

We collected d~~D~~ata on a range of confounding variables ~~were collected~~, such as ~~gross domestic product~~GDP per capita, smoking prevalence, climate data, illiteracy rate, and age composition (age > 65 years), together with travel movements from Wuhan and within-city movements (as ~~a~~ measures of compliance with social distancing). These variables were ~~used as~~ adjusted~~ing~~ ~~control variables~~ in the statistical analysis. The population size of each city and number of ~~,~~ COVID-19 deaths and hospital beds were not included in the model because of high multicollinearity with travel movements from Wuhan. The movements of approximately 4.~~three~~ 3 billion people during the Spring Festival holiday ~~trips~~ also induced uncoordinated changes in actual population sizes across cities (Simiao, Juntao et al. 2020). As expected, the number of COVID-19 cases in each city increased with increased ~~passenger~~ population inflow from Wuhan; m~~. M~~ore infections were reported in cities that had more travel~~l~~ers from Wuhan. Overall, we observed positive and significant associations between ~~both~~ confirmed cases of COVID-19 with historical air pollutant concentrations (Figure 1A). In the 324 cities (except Wuhan) that had data on air quality, an increase of 10 $\mu g/m^3$ in the NO_2, $PM_{2.5}$~~-~~, ~~or~~ and PM_{10} concentrations was associated with a 37.8% (95% confidence interval [CI]: 23.8%–52.0%), 32.3% (95% CI: 22.5%–42.4%), and ~~–or~~ 14.2% (7.9%–20.5%) increase in COVID-19 cases. We also examined the relationship between the number of severe COVID-19 cases and air pollutant levels. An increase of 10 $\mu g/m^3$ in NO_2, $PM_{2.5}$~~-~~, ~~or~~ and PM_{10} concentrations was associated with a 26.3% (95% CI: 11.7%–40.8%), 15.7% (95% CI: 6.3%–25.2%), and ~~–or~~ 6.43% (95% CI: 0.6%–12.2%) increase in severe COVID-19 cases. The results ~~are~~ were statistically significant and robust ~~to~~ in sensitivity analyses (Table 2 and Figure 3). The analysis was also carried out ~~for~~ using separate datasets. Cities were categorized ~~by~~ according to population size into small, medium, and large cities. There was no significant effect of long-term exposure to most of the –air pollutants~~pollution~~ on susceptibility to COVID-19 infection ~~vulnerability~~ when the data ~~was~~were stratified ~~into~~by population sizes. While, the effect persisted after stratification in NO_2 and $PM_{2.5}$ on confirmed COVID-19 cases among large cities and small cities, and the impact of PM_{10} in severe COVID-19 cases among large cities. This shows ~~how~~the importance of~~t~~ population ~~is~~ as a confounding variable in the analysis.~~The results might still be affected by population size, because air pollution is usually related to population. So, there is a predefined correlation between air pollutant concentration and population size.~~

~~4.~~ Discussion

In the present study, we ~~identified~~ clarified the association between long-term exposure to air pollution and vulnerability to COVID-19 ~~in~~ infection during the first epidemic wave ~~of~~ in China. The present results ~~are~~ were derived from a large, newly compiled and geocoded repository of population and epidemiological data relevant to COVID-19. Indeed, several studies have evaluated the association between air pollution exposure and COVID-19 risk (Copat, Cristaldi et al. 2020). Our finding ~~i~~was in line with studies based on large-scale nationwide data, including ~~in~~ from the US (Wu, Nethery et al. 2020), UK (Konstantinoudis, Padellini et al. 2020, Travaglio, Popovic et al. 2020, Travaglio, Yu et al. 2021), Italy (Conticini, Frediani et al. 2020, Fattorini and Regoli 2020), The Netherlands (Andree 2020), Spain, France, and Germany (Ogen 2020), ~~and~~ as well as various provinces of China (Yongjian, Jingu et al. 2020). ~~However,~~ Because the ~~size of the study and that of the~~ first COVID-19 wave ~~has been~~wereas contained in China, meaning~~t~~ that we were able to investigate the impact of historical air pollution on COVID-19 risk and severity.

In t~~T~~he present study, we found statistically significant evidence that an increase in long-term exposure to NO_2~~-~~, ~~or~~ $PM_{2.5}$~~-~~, or PM_{10} ~~corresponds~~ corresponded to an increase in the number of COVID-19 cases and severe infections. The findings are comparable to the results of previous studies in the US (Wu, Nethery et al. 2020) and Northern Europe (Andree 2020), where levels of $PM_{2.5}$ were also found to be strongly associated with COVID-19 incidence, after adjusting for multiple confounders. However, ~~this~~ ours ~~report is~~ was the first study to ~~employ~~ use ~~the~~ complete data ~~of~~ from the first wave of the COVID-19 epidemic in China and to identify ~~indicate~~ the association between long-term exposure to air pollution and COVID-19 risk, after controlling for many meteorological and demographic ~~characteristics~~ variables as well as human mobility data. T~~In addition, t~~he effects of NO_2 and PM_{10} exposure were also clearly shown ~~obvious~~ in our analysis model, which ~~is~~ was a relatively new result. The effects of different components of air pollutants on ~~the~~ COVID-19 should be further studied and confirmed.

~~Meanwhile~~O~~, o~~ur results highlight~~ed~~ the importance of air quality improvements ~~to~~ with respect to health in China. ~~On 23 January 2020, I~~in an attempt to ~~contain~~ control the epidemic, on 23 January 2020, non-essential travel was prohibited in and out of Wuhan city, a major transport hub and ~~conurbation~~ megacity of 11 million people. ~~Since then~~Subsequently~~, the whole of China has had implemented~~ , the highest level of emergency response was implemented throughout all of China, to reinforce ~~the~~ containment of the COVID-19 epidemic. Interventions included the closure of entertainment venues, ~~the~~ suspension of within-city public transport, and prohibition of travel to and from other cities ~~across~~ in China. These stringent~~Strong~~ intervention measures ~~have~~ significantly reduced ~~the~~ air pollution levels in ~~of~~ each city during this period (Le, Wang et al. 2020), which was confirmed in o~~. O~~ur monitoring results ~~confirmed this~~ (Figure 2). To some extent, ~~this is was actually a very good~~the interventions provided an excellent opportunity to ~~on~~ examine~~ing~~ the benefits of improved air quality (Chen, Wang et al. 2020). Reducing ~~concentrations of~~ air pollutant concentrations ~~s~~ would reduce the incidence of acute respiratory diseases~~,~~ and ~~the~~ people's susceptibility to numerous~~of~~ infectious diseases. Even ~~if there are were~~assuming that problems existed within the multiple interventions~~ problems~~, ~~such~~ these - results ~~are~~ were in line with ~~the~~ our expectations~~ations of our conclusion~~. Previous studies have demonstrated that exposure to air pollutants is associated with poorer lung function, often measured ~~by~~ using forced vital capacity and forced expiratory volume in 1 second (Ackermann-Liebrich U, Leuenberger P et al. 1997, Forbes LJ, Kapetanakis V et al. 2009, Urman R, McConnell R et al. 2014, Adam M, Schikowski T et al. 2015). Exposure to p~~P~~articulate matter– ~~is~~ ~~could~~may be associated with an increased risk of cardiopulmonary diseases (Chen, Yin et al. 2019), aggravation of the~~ed~~ case fatality rate of ~~severe acute respiratory syndrome~~ SARS (caused by SARS-CoV, another ~~type~~ strain of coronavirus) (Cui, Zhang et al. 2003), and ~~could~~ impaired ~~the~~ immune response (Wei and Tang 2018). Oxidant pollutants could also damage the innate immune respons~~ed~~ and increase ~~the~~ host susceptibility ~~of~~ to viruses ~~through~~ by interfering with ~~reflecting~~ the function of macrophages(Karan, Ali et al. 2020, Qu, Li et al. 2020) ~~(Qu, Li et al. 2020);(Karan, Ali et al. 2020)~~. Nitrogen oxides (NO_X) ~~can~~ would cause inflammatory responses and worsen ~~the~~ pre-existing lung inflammation~~ situation which~~, resulting ~~to~~ in a direct effect on the risk of respiratory diseases (Takahashi Y, Mochitate K et al. 1986, Conticini, Frediani et al. 2020), which is ~~(~~also shown in the Comparative Toxicogenomics Database (~~,~~http://ctdbase.org). ~~Nitrogen oxide~~NO_2 is primarily produced by traffic and factories~~,~~ and is less influenced by climatice conditions, so there were reductions in ~~both~~ the concentration of NO_X ~~nitrogen oxides and~~with a decline in within-city movements during the COVID-19 outbreak throughout ~~in cities of~~ China. Increased O_3 and ~~ozone or sulfur dioxide~~ SO_2 concentrations were associated with lower COVID-19 risk, which ~~is~~ was also consistent with previous studies (Travaglio, Popovic et al. 2020, Yongjian, Jingu et al. 2020). However, the mechanisms underlying the impact of these pollutants on COVID-19 risk remain uncertain.

The association between long-term exposure to air pollution and vulnerability to COVID-19 may be affected by some confounders. We considered many variables ~~to~~ for ~~be~~ inclusion~~ded~~ in the initial model, such as population, inflow from Wuhan, and the number of COVID-19 deaths and hospital beds. However, ~~due~~ owing to the collinearity ~~between~~ among these four variables, we retained only one of these ~~most important~~ variables. We believe that in the first COVID-19 wave, the population inflow from Wuhan ~~is~~ ~~should be~~was the most important factor affecting ~~the~~ development of the epidemic. ~~So~~Therefore, only the variable of inflow from Wuhan was ~~kept~~ retained and the other three were eliminated from the final model. However, we ~~think~~ ~~thought~~believe that the variable of population is also ~~should also be~~ ~~is~~ very important; thus, a~~. A~~ hierarchical analysis for the population variable ~~variable~~ was ~~done~~ conducted separately. We found that the association between long-term exposure to air pollutants and vulnerability to COVID-19 ~~was~~ differed among ~~nt in~~ different-sized cities. In ~~the~~ large-sized cities, the association was more obvious, which may be ~~due~~ owing to better health care, better case reporting, and better testing policies in ~~the~~ large cities. Therefore, the effect of population size ~~should be~~is complex and needs further analysis.

~~During the first COVID-19 wave,~~ As with other novel infectious diseases, t~~t~~here were many challenges ~~with~~ in ~~its~~ the diagnosis of COVID-19 during the first epidemic wave~~, just like other novel infectious diseases~~ (Arons, Hatfield et al. 2020, Li, Geng et al. 2020). Concern has been expressed about the sensitivity and specificity of the tests initially used to identify people infected with ~~coronavirus~~SARS-CoV-2. The performance ~~in~~ of the detection methods has improved over time (Carter, Garner et al. 2020). ~~Meanwhile,~~At the same time, there is a lack of adequate testing in most countries, and treatment of patients with COVID-19 in many jurisdictions is inadequate owing to overburdened health systems. As a result, many cases and deaths that ~~should have been~~ were attributable~~ted~~ to COVID-19 have not been confirmed. These issues may have some influence on the findings of this study. For example, this situation~~it~~ would lead to ~~the~~ inaccuracies in ~~y of~~ the number of confirmed ~~COVID-19~~ cases or severe cases of COVID-19 infection, which would cause some bias in the results. T~~In addition, t~~his ~~also~~ may also be a ~~one of the~~ reason~~s~~ ~~for~~ that rates of ~~higher~~ greater severity of the disease are consistently lower. ~~But~~ However, early studies ~~of~~ during the epidemic can draw on the results of a ~~more~~ pure transmission model. The present study focused on the association between air pollution and COVID-19 in the first wave ~~from~~ in Wuhan, ~~in~~ China. The variables included important human mobility data, such as inflow from Wuhan and peak time of inflow from Wuhan. These data~~It~~ would well reflect some important scientific problems in the early stages of ~~the spread of~~an outbreak of a new infectious disease~~s~~.

Several important caveats are worth mentioning. First, the data included here were all from mainland China; i~~. I~~t is therefore ~~not~~ unclear whether the findings can be generalized to other countries without data on historic air pollution exposure. Second, there are currently no high-quality records at city level ~~of~~ regarding severe COVID-19 infections and ICU admissions, although we have attempted to fill thise gap by using province-level reports. Third~~ly~~, ~~the data of~~ air pollution data from ambient air quality stations across China do not necessarily reflect exposure to indoor air pollution; ~~and~~ this may therefore bias the results. Finally, we do not know the exact number of cases because ~~of~~ we do not know the number of asymptomatic and mildly-symptomatic cases that may not have been recorded. These data will not be available until there has been a systematic survey of infection (e.g., ~~by~~ via serological testing) across China. However, we ~~have~~ reported a national-level disease pattern covering 324 cities and its potential association with long-term exposure to air pollutants.

~~5.~~Conclusions

In t~~T~~he present study, we found a significant positive association between long-term exposure levels ~~of~~ to PM$_{2.5}$, PM$_{10}$, NO$_2$~~-~~, and ~~COVID-19~~ the risk and severity of COVID-19 infection in China. ~~It~~ Our findings suggest~~ed~~ that air pollution may be related to ~~the~~ population vulnerability to COVID-19. Interventions to control the COVID-19 outbreak in China successfully reduced air pollution levels and potentially prevented further cases of acute respiratory disease. Improved~~Fine~~ air quality may be conducive to reducing~~e~~ the hazards of respiratory infectious diseases. The link between COVID-19 and air pollution deserves ~~a~~ more definitive and global data analysis.

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Declaration of competing interests

The authors declare that they have no known competing financial interest or personal relationships that could have ~~appeared to~~ influenced the work reported in this paper.

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Table 1.– Databases and sources of coronavirus disease 2019 (COVID-19) and air pollution data

Database	data provider	Source
COVID-19		
Confirmed COVID-19 cases	Provincial Health Committees which contained data of each city	Official website of health commission of 34 provincial-level administrative units and 342 city-level units
Severe COVID-19 cases	Provincial Health Committees which contained data of each city	Official website Health commission of 34 provincial-level
COVID-19 deaths	Provincial Health Committees which contained data of each city	Official website of health commission of 34 provincial-level administrative units and 342 city-level units
Human mobility data		
Outflow from Wuhan	Baidu location-based services mobile phone data provided by the telecommunications operators	https://qianxi.baidu.com/
Within-city movements	The activities index of human mobility with a city	https://qianxi.baidu.com/
Meteorological data		
$PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3	China National Environmental Monitoring Centre,2015-2019	http://www.cnemc.cn/
Temperature	Mean Temperature of Warmest/Coldest Quarter (2015-2019)	https://www.worldclim.org/data/bioclim.html
Rainfall	Precipitation of Warmest/Coldest Quarter (2015-2019)	https://www.worldclim.org/data/bioclim.html
Relative Humidity	National Meteorological Information Center (CMA Meteorological Data Center, 2015-2019)	http://data.cma.cn/
Demographic data		
Gross domestic product (GDP)	China City Statistical Yearbook 2019	http://www.stats.gov.cn/tjsj/ndsj/2019/indexeh.htm
Age structure	Sixth National Population Census of the People's Republic of China (2013)	http://www.stats.gov.cn/tjsj/pcsj/rkpc/6rp/indexch.htm
Smoking and second-hand smoking prevalence	Chinese National Nutrition and Health Survey (NNHS)	PMID: 24698853
Hospital beds	China City Statistical Yearbook 2019	http://www.stats.gov.cn/tjsj/ndsj/2019/indexeh.htm
Illiteracy rate	Sixth National Population Census of the People's Republic of China (2013)	http://www.stats.gov.cn/tjsj/pcsj/rkpc/6rp/indexch.htm

COVID-19, coronavirus disease 2019; $PM_{2.5}$, particulate matter ≤ 2.5 μm; PM_{10}, particulate matter ≤ 10 μm; SO_2, sulfur dioxide; CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; CMA, China Meteorological Administration.

Table 2.~~–~~ Impact of historical air pollution exposure on cases of COVID-19 ~~cases~~

	Confirmed COVID-19 cases			**Severe COVID-19 cases**		
Covariates	Coefficient (95%CI)	std	P	Coefficient (95%CI)	std	P
NO_2	0.378（0.238,0.52）	0.072	<0.001	0.263(0.117,0.408)	0.074	<0.001
Intercept	-1.697（-3.436,0.021）	0.882	0.055	-1.919(-3.437,-0.401)	0.771	0.013
Inflow from Wuhan	0.007（0.007,0.008）	<0.001	<0.001	0.016(0.013,0.019)	0.002	<0.001
Within-city movements	-1.14（-1.382,-0.901）	0.123	<0.001	-0.853(-1.098,-0.609)	0.124	<0.001
Peak of inflow from Wuhan	0.175（0.133,0.218）	0.022	<0.001	0.086(0.043,0.13)	0.022	<0.001
Mean temperature of coldest quarter	-0.023（-0.045,-0.001）	0.011	0.040	0.006(-0.014,0.027)	0.010	0.528
Relatively humidity	0.048（0.029,0.067）	0.010	<0.001	0.028(0.012,0.045)	0.008	0.001
Illiteracy rate	0.053（0.014,0.09）	0.019	<0.001	0.0188(-0.017,0.055)	0.018	0.305
$PM_{2.5}$	0.323（0.225,0.424）	0.051	<0.001	0.157(0.063,0.252)	0.048	0.001
Intercept	-1.237（-2.841,0.329）	0.809	0.128	-1.313(-2.689,0.062)	0.699	0.061
Inflow from Wuhan	0.007（0.006,0.007）	<0.001	<0.001	0.015(0.012,0.018)	0.002	<0.001
Within-city movements	-1.376（-1.617,-1.139）	0.122	<0.001	-0.961(-1.192,-0.731)	0.117	<0.001
Peak of inflow from Wuhan	0.137（0.096,0.179）	0.021	<0.001	0.077(0.033,0.121)	0.022	0.001
Mean temperature of coldest quarter	-0.003（-0.027,0.022）	0.012	0.790	0.01(-0.01,0.03)	0.010	0.329
Relatively humidity	0.052（0.032,0.071）	0.010	<0.001	0.026(0.01,0.042)	0.008	0.002
Illiteracy rate	0.049（0.008,0.087）	0.020	0.016	0.019(-0.017,0.056)	0.018	0.293
PM_{10}	0.142（0.079,0.205）	0.032	<0.001	0.0643(0.006,0.122)	0.032	<0.001
Intercept	-1.183（-3.023,0.609）	0.927	0.203	-1.183(-2.861,0.217)	0.927	0.203

Inflow from Wuhan	0.007（0.006,0.007）	<0.001	<0.001	0.007(0.012,0.018)	<0.001	<0.001
Within-city movements	-1.346（-1.604,-1.092）	0.131	<0.001	-1.346(-1.208,-0.742)	0.131	<0.001
Peak of inflow from Wuhan	0.148（0.104,0.194）	0.023	<0.001	0.148(0.037,0.126)	0.023	<0.001
Mean temperature of coldest quarter	-0.009（-0.033,0.016）	0.013	0.455	-0.009(-0.011,0.03)	0.013	0.455
Relatively humidity	0.054（0.032,0.076）	0.011	<0.001	0.054(0.012,0.046)	0.011	<0.001
Illiteracy rate	0.046（0.003,0.086）	0.021	0.033	0.046(-0.021,0.053)	0.021	0.033

COVID-19, coronavirus disease 2019; $PM_{2.5}$, particulate matter ≤ 2.5 μm; PM_{10}, particulate matter ≤ 10 μm; NO_2, nitrogen dioxide; CI, confidence interval.

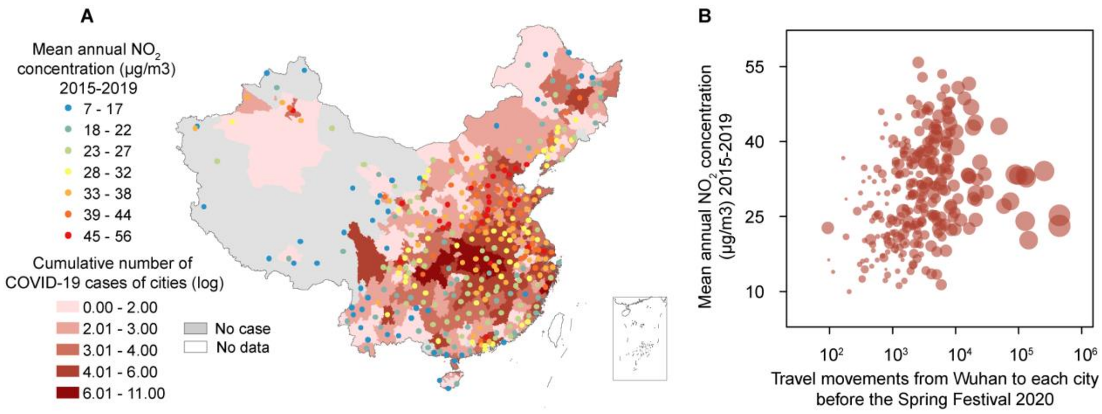

Figure 1. Air pollution exposure, coronavirus disease 2019 (COVID-19) cases, and travel movements in 324 cities of China during Spring Festival 2020. (A) Distribution of cities with data on nitrogen dioxide (NO_2) concentrations ~~–~~and COVID-19 cases. S~~The s~~hading from light red to dark red represents ~~the ~~cumulative number of confirmed COVID-19 cases in each city, from low to high, respectively, from 31 December 2019 to 6 March 2020; ~~–(~~white area represents no data, and grey area represents no cases~~)~~. Points colo~~u~~red from blue to red represent ~~the ~~historic mean annual NO_2~~–~~ concentrations (µg/m^3), from low to high, respectively, during January 2015 and December 2019, ~~before ~~prior to the COVID-19 ~~–~~epidemic. (B) Association between the cumulative number of confirmed cases, the number of human movements from Wuhan to each city, and historic mean annual NO_2 concentration. The area of the circles represents the cumulative number of cases reported by 6 March 2020.

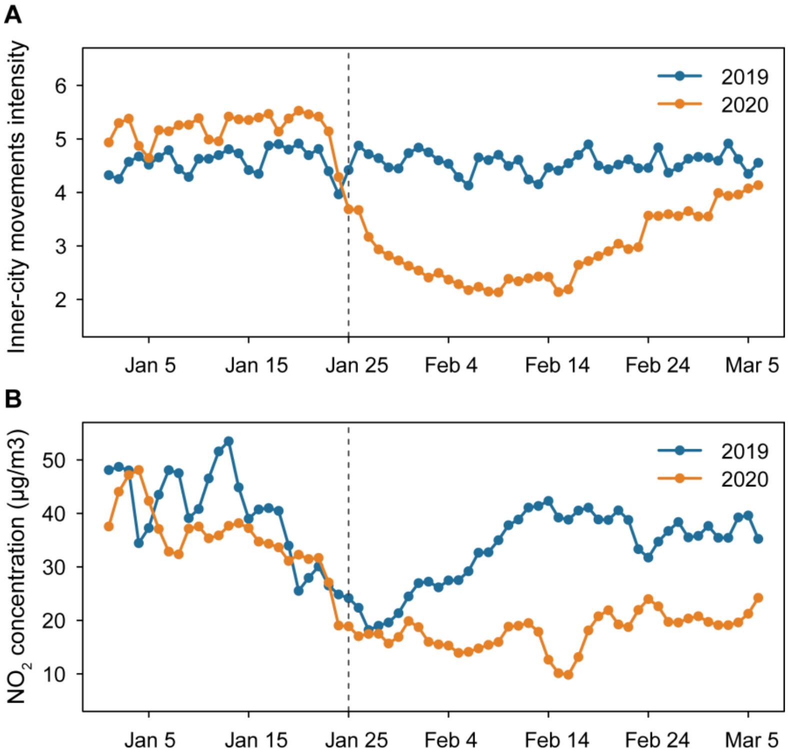

Figure 2. (A) Average within-city movement intensity and (B) air pollutant concentration in 324 cities ~~in~~ of China during the 2020 COVID-19 outbreak (orange line), compared with the same period in 2019 (blue line).

NO_2, nitrogen dioxide.

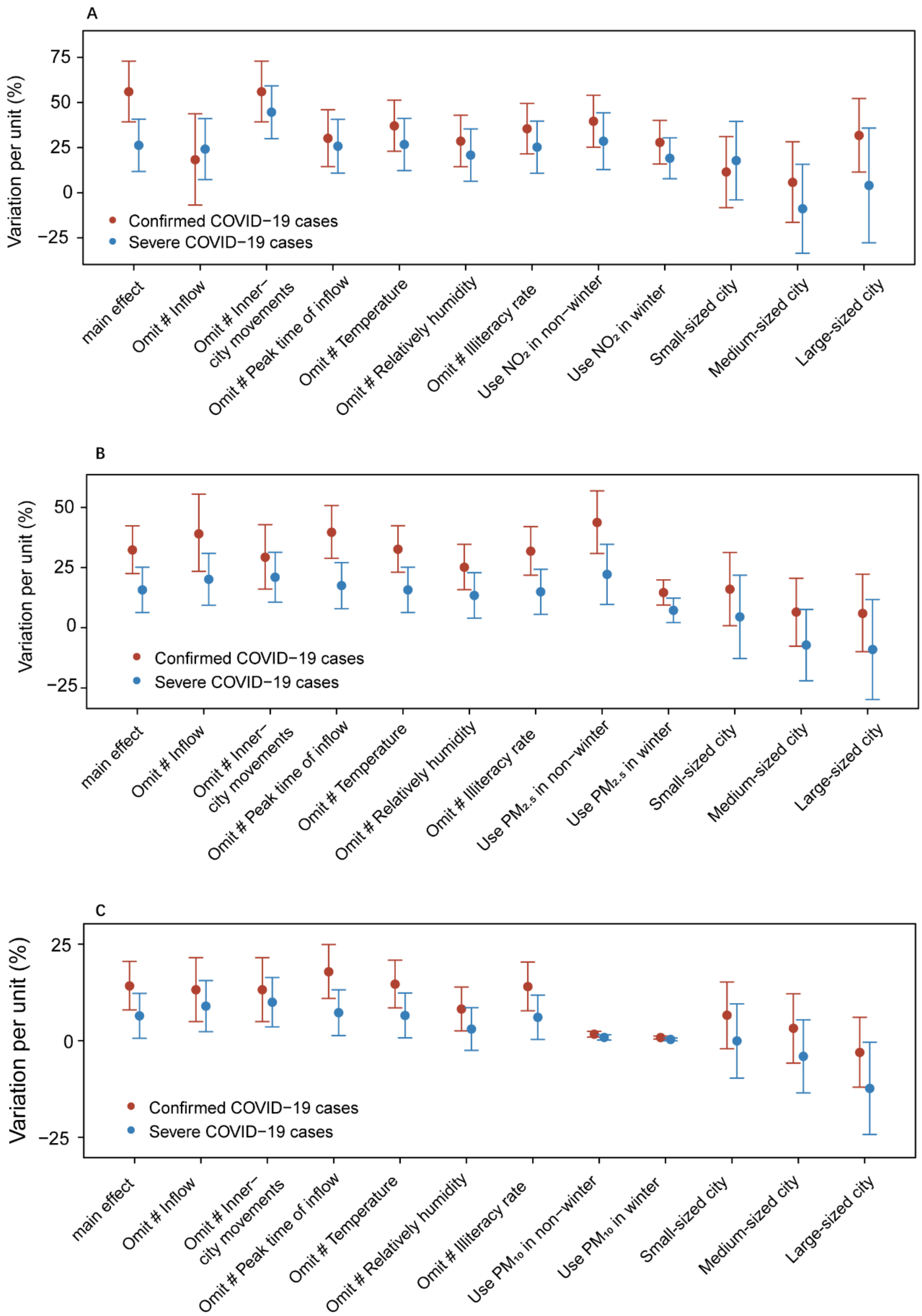
A
Variation per unit (%)
75
50
25
0
−25
Confirmed COVID−19 cases
Severe COVID−19 cases
main effect
Omit # Inflow
Omit # Inner−city movements
Omit # Peak time of inflow
Omit # Temperature
Omit # Relatively humidity
Omit # Illiteracy rate
Use NO_2 in non−winter
Use NO_2 in winter
Small-sized city
Medium-sized city
Large-sized city
B
Variation per unit (%)
50
25
0
−25
Confirmed COVID−19 cases
Severe COVID−19 cases
main effect
Omit # Inflow
Omit # Inner−city movements
Omit # Peak time of inflow
Omit # Temperature
Omit # Relatively humidity
Omit # Illiteracy rate
Use $PM_{2.5}$ in non−winter
Use $PM_{2.5}$ in winter
Small-sized city
Medium-sized city
Large-sized city
C
Variation per unit (%)
25
0
−25
Confirmed COVID−19 cases
Severe COVID−19 cases
main effect
Omit # Inflow
Omit # Inner−city movements
Omit # Peak time of inflow
Omit # Temperature
Omit # Relatively humidity
Omit # Illiteracy rate
Use PM_{10} in non−winter
Use PM_{10} in winter
Small-sized city
Medium-sized city
Large-sized city

Figure 3. Variation per unit and 95% confidence intervals, (A) NO_2, (B) $PM_{2.5}$ ~~a~~, and (C) PM_{10}. The variation per unit (VPU) = [exp(variable coefficient) – 1] × 100%. The VPU can be interpreted as the percentage increase in the number of COVID-19 cases associated with a 10 $\mu g/m^3$ increase in long-term average NO_2 and $PM_{2.5}$. The VPU from the main analysis was adjusted ~~by~~ for confounding factors. In the sensitivity analyses, we omitted each confounding factor separately, and used seasonal air pollutant concentrations.

COVID-19, coronavirus disease 2019; $PM_{2.5}$, particulate matter ≤ 2.5 µm; PM_{10}, particulate matter ≤ 10 µm; NO_2, nitrogen dioxide.