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Association between NO₂ cumulative exposure and influenza prevalence in mountainous regions: A case study from southwest China

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ABSTRACT

While accumulating evidence shows that air pollution exposure is an important risk factor to influenza prevalence, their association has been inadequately investigated in mountainous regions with dense populations and high humidity. We aim to estimate the association and exposure-outcome effects between exposure to nitrogen dioxide (NO₂) and influenza prevalence in a mountainous region with a dense population and high humidity. We investigated 14,993 patients with confirmed influenza cases from January 2013 to December 2017 in Chongqing, a mountainous city in southwest China. We developed distributed lag non-linear models with quasi-Poisson link to take into account the lag and non-linear effects of NO₂ exposure on influenza prevalence. We estimated that the cumulative effect of a 10 μg/m³ increase in NO₂ with seven-day lag (i.e., summing all the contributions up to seven days) corresponded to relative risk of 1.24 (95% CI: 1.17–1.31) in daily influenza prevalence. Comparing to annual mean of the World Health Organization air quality guidelines of 40 μg/m³ for NO₂, we estimated that 14.01% (95% CI: 10.69–17.08%) of the influenza cases were attributable to excessive NO₂ exposure. Our results suggest that NO₂ exposure could worsen the risk of influenza infection in this mountainous city, filling the gap of relevant researches in densely populated and mountainous cities. Our findings provide evidence for developing influenza surveillance and early warning systems.

1. Introduction

Respiratory infection due to viral infections caused by severe acute respiratory syndrome (SARS) virus, coronavirus (COVID-19) and influenza virus is one of the most common underlying causes of morbidity and mortality (WHO, 2018a; WHO, 2020a). These viruses enter into human body through multiple pathways such as aerosol transmission (Lowen and Palese, 2009; Shiu et al., 2019) and can induce large number of infections and subsequent mortality (WHO, 2003; WHO, 2020a). Respiratory infection due to influenza is recognized as one of the most serious threats to public health around the world because it took 290,000 to 650,000 human lives per year during 1999–2015 (Luliano et al., 2018). Severe air pollution in industrialized regions of the world can exacerbate respiratory infection (Jiang et al., 2016), and the World

Abbreviations: NO₂, Nitrogen Dioxide; RR, Relative Risk; WHO, World Health Organization; AQG, Air Quality Guideline; CI, Confidence Intervals; SARS, Severe Acute Respiratory Syndrome; AF, Attributable Fraction; AN, Attributable Number; SO₂, Sulfur Dioxide; O₃, Ozone; CO, Carbon Monoxide; PM₂.₅, Fine Particulate Matter; PM₁₀, Respirable Particulate Matter; CCDCP, Chongqing Center for Disease Control and Prevention; CSDCP, China Information System for Disease Control and Prevention.

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Health Organization (WHO) estimated that seven million people died of air pollution worldwide annually (WHO, 2020b). Given the magnitude of impact of pollution and respiratory infection on public health, it is thus crucial to investigate the relationship between an exemplary respiratory disease, namely influenza, and air pollution.

Exposure to air pollution is associated with the increase in the risk of respiratory diseases (Pannullo et al., 2017; Xu et al., 2013), as air pollution can affect the respiratory tract via inhalation, increasing the risk for infection (Wong et al., 2010). In particular, exposure to NO\(_2\) causes oxidative stress and generates free radicals that can subsequently damage lung’s epithelial cells, aggravate pulmonary inflammation, weaken macrophage phagocytosis, and increase susceptibility to viruses (Cienciewicki and Jaspers, 2007; Purvis and Ehrlich, 1963). Elevated NO\(_2\) concentration has stronger association with patients diagnosed with respiratory diseases (Pannullo et al., 2017; Tao et al., 2014).

For assessing the impact of pollution exposure on human health, mortality and morbidity data are commonly used as response variables in association analyses (Gasparrini et al., 2015). In an exposure-response analysis, generalized additive models (GAM) were developed to model the environmental exposures to accommodate potential non-linear effects of environmental factors (Ravinda et al., 2019). In addition, air pollution was reported to exhibit lag effect on health outcomes associated with cumulative exposure rather than just current exposure (Luo et al., 2018). Distributed lag non-linear models (DLNM) can simultaneously model the nonlinear and lag effects (Gasparrini et al., 2010), accommodating the additional temporal dimension in the exposure-response relationship.

This study aims to estimate the association between NO\(_2\) exposure and influenza prevalence in Chongqing, a densely populated and highly humid mountain city in southwest with a population of approximately 31 million (NBSC, 2019). Considering the potentially combination of nonlinearity and lag effects in the exposure-outcome relationship, we coupled the GAM with the DLNM model to calculate relative risk (RR), attributable fraction (AF), attributable number (AN), and relative risk (RR) in order to quantify the potential effects of NO\(_2\) exposure (Gasparrini and Leone, 2014). We hope findings from this can help to advance the understanding of the adversary effects air pollution has on health and the manifestation of influenza in the context of air pollution. Meanwhile, we also hope the results here can provide scientific support for public health and clinical interventions to mitigate environmental impact on respiratory illness.

2. Materials and methods

2.1. Study area

Chongqing is a mountainous megacity situated on the eastern margin of Sichuan Basin and a major manufacturing, economic, transportation center in the upstream of the Yangtze River (Fig. 1). Chongqing, nick-named a “Fog City”, experiences over 100 days of foggy days per year (Climate-data, 2020), and has a humid subtropical climate and extremely slow wind speeds, with an annual average relative humidity (RH) of 75.10% during 2013–2017 (CMA, 2020).

2.2. Data preparation

The Chongqing Center for Disease Control and Prevention (CCDCP) monitors the infectious disease surveillance subsystem of the China Information System for Disease Control and Prevention (CISDCP). We included the clinical and confirmed influenza cases from outpatients and inpatients during 2013–2017, which included records from 122 secondary and tertiary hospitals in Chongqing (Fig. 1). The distances between these hospitals and their nearest air quality stations are 14.1 ± 19.5 (mean ± standard deviation) km. Our study protocol was approved by the CCDCP. Since all the data are aggregated at the urban level, informed consent was waived.

We used daily data of air quality and weather conditions during 2013–2017 in statistical analysis: concentration data of NO\(_2\), SO\(_2\), O\(_3\), CO, PM\(_{2.5}\), and PM\(_{10}\) were retrieved from 17 air quality stations of the Ministry of Ecology and Environment of China (MEEC, 2020), and seven meteorological variables (relative humidity, precipitation, temperature, sunshine duration, atmospheric pressure, wind speed, and evaporation) were obtained from 12 weather stations of the China Meteorological Administration (CMA, 2020). The daily concentrations were averaged from the hourly concentration data with missing rates of 3.2, 2.0, 2.6, 2.5, 3.6 and 6.3% for NO\(_2\), SO\(_2\), O\(_3\), CO, PM\(_{2.5}\), and PM\(_{10}\) respectively. The days with missing rates exceeding 25% were excluded, resulting in the daily concentration dataset with missing rates of 1.8, 0.7, 1.2, 1.2, 1.9, and 2.3% for NO\(_2\), SO\(_2\), O\(_3\), CO, PM\(_{2.5}\), and PM\(_{10}\), respectively.

2.3. Statistical analysis

Given the potentially non-linear and lag effects of air pollutants on the influenza prevalence, we developed a DLNM model (with natural cubic spline) and quasi-Poisson link function to examine the association

![Fig. 1. Locations of (a) air quality and weather stations and (b) hospitals in Chongqing.](image-url)
between the NO\textsubscript{2} cumulative exposure and the influenza prevalence (Gasparrini, 2011). In our analysis, we approximated NO\textsubscript{2} exposure with NO\textsubscript{2} concentrations reported by pollution monitors. The factor variable of “month of the year” was included in the model as the virus factor given the seasonal pattern of flu outbreaks (Qiu et al., 2019). Meteorological conditions were added to the model as confounding factors. The model equations are shown below:

\[
Y_t \sim P(\mu_t) \quad (1)
\]

\[
E(Y_t) = \mu_t \quad (2)
\]

\[
\log(\mu_t) = \alpha + \beta_1 X_{t1} + \beta_2 X_{t2} + \cdots + \beta_l X_{tl} + \gamma T + s(H) + s(P) + s(W) + s(E) + s(S) + f(M) \quad (3)
\]

where \(Y_t\) represents the estimated daily number of influenza cases due to NO\textsubscript{2} exposure on day \(t\); \(\mu_t\) is the mean of \(Y_t\); \(\alpha\) is the intercept; \(X_{tl}\) represents the cross-basis function with the exposure \(x\) and its lag \(l\) effects; \(\beta\) is vector of coefficients; \(s()\) represents the natural cubic spline function; \(T\) is the mean temperature; \(H\) is the relative humidity; \(P\) is the mean precipitation; \(W\) is the mean atmospheric pressure; \(M\) is the mean wind speed; \(E\) is the mean evaporation; \(S\) is the mean sunshine duration; and \(M\) is the month of the year. The model parameters such as the degree of freedoms were optimized based on the lowest generalized cross validation (GCV) score (Dominici et al., 2004; Peng et al., 2006).

In order to test the robustness of the model, we randomly separated the study cases into a training set and a validation set, which accounted for 90% and 10% of the data, respectively. The training set was used to parameterize the model, and then its predictions were compared against the validation set. The predictive performance of the model was evaluated with commonly used statistical measures, including the correlation coefficient \((R)\), root mean square error \((RMSE)\), and mean absolute deviation \((MAD)\).

We developed two-pollutant models and conducted stratified analyses to evaluate potentially additive or synergistic effects of combined exposure to NO\textsubscript{2} and another air pollutant (i.e., SO\textsubscript{2}, O\textsubscript{3}, CO, PM\textsubscript{2.5}, or PM\textsubscript{10}). For the two-pollutant models, the non-linear and lag effects of two pollutants were modeled as follows:

\[
\log(\mu_t) = \alpha + \beta_1 X_{t1} + \gamma_1 X_{t12} + s(T) + s(H) + s(P) + s(W) + s(E) + s(S) + f(M) \quad (4)
\]

where \(X_{t12}\) represents the cross-basis function with the exposure \(y\) and its lag \(l\) effects for the second pollutant (NO\textsubscript{2} is the first pollutant); \(\gamma\) is vector of coefficients; and please refer to Eq. (3) for the definitions of the other variables. The stratified analyses were conducted by air pollutant concentration level. Using CO as an example, we divided the whole dataset into three groups (i.e., low, moderate, and high groups) based on the 1/3 and 2/3 quantiles of CO concentrations. For each group, we developed a model with Eq. (3) and estimated the RR. We then compared the RR values from these three groups in order to evaluate the potentially synergic effects between CO and NO\textsubscript{2} exposures. The same procedure was repeated for SO\textsubscript{2}, O\textsubscript{3}, PM\textsubscript{2.5}, and PM\textsubscript{10} in turn.

Furthermore, we evaluated the associations between the cumulative NO\textsubscript{2} exposure and influenza prevalence with the DLNM model from both backward and forward perspectives (Gasparrini and Leone, 2014). From the backward perspective, we presumed that the risk on day \(t\) was the cumulative effect of the past exposure at times \(t - l_0, \ldots, t - L\). From the forward perspective, we viewed the future risks from the present exposure by considering exposure on day \(t\) caused risks on days \(t + l_0, \ldots, t + L\).

\[
b_{AF_{t+1}} = 1 - \exp \left( -\sum_{i=l_0}^{L} \beta_{AF_{t+1}} \cdot \Delta x \right) \quad (5)
\]

\[
b_{AN_{t+1}} = b_{AF_{t+1}} \cdot n_i \quad (6)
\]

where \(b_{AF_{t+1}}\) represents the AF of influenza for exceeding exposure \(\Delta x\) at time \(t\) and \(b_{AN_{t+1}}\) is the AN of inflammuses, from backward perspective; \(l\) is between \(l_0\) and \(L\) and represents the number of day; with \(n_i\) as the number of influenza cases at time \(t\); \(\beta\) indicates the risk associated with the exposure \(\Delta x\) at time \(t\), and it corresponds to the logarithm of RR; \(\Delta x\) is the concentration difference between the NO\textsubscript{2} observation and the reference value (i.e., WHO air quality guideline of 40 \(\mu\text{g/m}^3\)).

\[
f_{AF_{t+1}} = 1 - \exp \left( -\sum_{i=l_0}^{L} \beta_{AF_{t+1}} \cdot \Delta x \right) \quad (7)
\]

\[
f_{AN_{t+1}} = f_{AF_{t+1}} \cdot \sum_{i=l_0}^{L} n_i + f \cdot L - l_0 + 1 \quad (8)
\]

where \(f_{AF_{t+1}}\) represents the AF of influenza for exceeding exposure \(\Delta x\) at time \(t\), and \(f_{AN_{t+1}}\) is the AN of inflammuses from the forward perspective.

We conducted all statistical analyses in R version 3.4.0 (R Development Core Team, Vienna, Austria), with packages of \texttt{dlm} (Gasparrini, 2011) and \texttt{mgcv} (Wood, 2011).

3. Results and discussion

3.1. Exploratory analyses

We analyzed 14,993 confirmed influenza cases between 2013 and 2017 in Chongqing. During the study period, daily average concentrations of O\textsubscript{3}, PM\textsubscript{2.5}, PM\textsubscript{10}, SO\textsubscript{2}, NO\textsubscript{2}, and CO were 41.5 ± 28.5 \(\mu\text{g/m}^3\), 55.9 ± 34.6 \(\mu\text{g/m}^3\), 86.5 ± 47.5, 19.2 ± 12.2 \(\mu\text{g/m}^3\), 41.4 ± 12.2 \(\mu\text{g/m}^3\), and 1.0 ± 0.3 mg/m\(^3\), respectively (Table 1). The average concentrations of PM\textsubscript{2.5}, PM\textsubscript{10}, and NO\textsubscript{2} exceeded the WHO air quality guideline of 10, 20, and 40 \(\mu\text{g/m}^3\), respectively (WHO, 2005). Influenza outbreaks occurred frequently in winter-spring while only occasionally in summer, with weak seasonal repetition over the years (Fig. 2). NO\textsubscript{2} exposure and influenza cases showed a slight upward trend simultaneously. Due to the transmission pattern of influenza virus, the influenza outbreak has a short duration (Brankston et al., 2007). High NO\textsubscript{2} concentrations coincided with these influenza outbreaks based on their correlation coefficients (Fig. S1). The influenza outbreak showed significant correlation with the NO\textsubscript{2} concentrations (\(r = 0.20, P < 0.05\)) and CO concentrations (\(r = 0.12, P < 0.05\)).

It is noteworthy that all of the air quality stations were in the western and low-elevation part of the study area, where the majority of the population and hospitals were located (Fig. 1). By assuming that all individuals shared the same levels of air pollution exposure, we averaged the observations from all of those stations. Nevertheless, considering the limited number and spatially uneven distribution of the air quality stations, the exposure assessment for the whole population would be biased to a certain extent. Especially, the exposure levels of the people living in the eastern and high-elevation part of the study area would be overestimated. This issue of exposure misclassification could be resolved in the future by utilizing full-coverage datasets of air...
pollution that were derived from satellite retrievals (Hodgson et al., 2015; Zhan et al., 2018).

The coupled DLNM model is better than single model in simulating the relationship between influenza prevalence and NO$_2$ exposure. It should be noted that the influenza cases might not be occurring independently because of the infectious nature of influenza, as a result, the DLNM model may result in biased estimation. For future studies, a mixed-effects model with a specified correlation structure could resolve the issue of dependence (Zuur et al., 2009). At the same time, mechanistic models could be employed to simulate the viral factor, such as the Predictive Fitness Model that simulated the evolution of the virus (Luksza and Lääsigg, 2014), and the Propagation Mechanism Model that considered the propagation dynamics of the virus (Heesterbeek et al., 2015). While more efforts would be required to refine the modeling technique, results of current the DLNM model reflect the distributed lag and non-linear effects and provide a baseline for further studies.

3.3. Cumulative effect

The single lag-specific effects and cumulative effect of NO$_2$ exposure showed distinctive variations within the same lag period. The lag-response curve and the cumulative association curve for 10 µg/m$^3$ increase in NO$_2$ within seven-day lag show the quantitative relationship between the NO$_2$ exposure and influenza prevalence (Fig. 4). The RR fluctuated along the time dimension in a non-linear decline manner at the single lag-specific effects (i.e., noncumulative effects). With an increase of 10 µg/m$^3$ NO$_2$ exposure, the RR on the first day was as high as 1.125 and then gradually declined to 1.002. The influenza prevalence on a certain day is not only caused by the NO$_2$ exposure on that day, but also cumulative effect of exposure over a period of time, for instance seven days in the present study. Consequently, the cumulative RR increased sharply and then slowly increased during the first to the sixth day (Fig. 4b). During the seven-day lag period, the cumulative RR associated with an increase of 10 µg/m$^3$ exposure increased to 1.24 (95% CI: 1.17–1.31). The slight increase in the second half of the lag period might be associated with the incubation period of influenza virus, which generally ranged from one to four days (WHO, 2018b). The rebound of influenza prevalence after the incubation period would be accompanied with the slight increase of RR.

| Variable$^a$ | Mean | SD | Min | 25% | 50% | 75% | Max |
|--------------|------|----|-----|-----|-----|-----|-----|
| O$_3$ (µg/m$^3$) | 41.45 | 28.46 | 3.10 | 18.50 | 36.10 | 57.90 | 216.50 |
| PM$_{10}$ (µg/m$^3$) | 55.90 | 34.55 | 7.50 | 31.90 | 45.60 | 69.10 | 214.50 |
| PM$_{2.5}$ (µg/m$^3$) | 86.46 | 47.52 | 13.00 | 53.20 | 76.45 | 106.00 | 296.60 |
| SO$_2$ (µg/m$^2$) | 19.19 | 12.20 | 4.10 | 11.00 | 15.30 | 23.60 | 73.80 |
| NO$_2$ (µg/m$^2$) | 41.37 | 12.17 | 13.10 | 32.60 | 40.00 | 48.60 | 91.90 |
| CO (mg/m$^3$) | 1.04 | 0.28 | 0.30 | 0.80 | 1.00 | 1.20 | 2.80 |
| Temperature (°C) | 16.78 | 7.46 | -0.40 | 10.00 | 17.25 | 22.80 | 33.70 |
| Precipitation (mm) | 3.23 | 7.47 | 0.00 | 0.00 | 0.20 | 2.70 | 65.50 |
| Humidity (%) | 75.11 | 9.47 | 41.30 | 68.70 | 75.00 | 82.00 | 98.00 |
| Pressure (hPa) | 953.64 | 7.77 | 927.10 | 947.50 | 953.30 | 959.80 | 976.60 |
| Wind speed (m/s) | 1.80 | 0.53 | 0.30 | 1.40 | 1.80 | 2.10 | 4.20 |
| Evaporation (mm) | 2.26 | 1.36 | 0.10 | 1.20 | 1.80 | 3.10 | 7.20 |

$^a$ Daily average.

Table 1

Summary statistics of air pollutants and weather parameters in Chongqing, 2013–2017.
Fig. 2. Time series plot of daily (a) influenza cases, (b) NO$_2$ exposure levels, (c) mean temperature, and (d) mean relative humidity.
The cumulative RR of 1.24 (95% CI: 1.17–1.31) estimated in the present study was comparable with the previous studies on the association between influenza-like respiratory diseases and air pollution exposure (Chen et al., 2017; Lin et al., 2013; Xu et al., 2013). A study of evaluating the impact of PM$_{2.5}$ (an increase of 10 μg/m$^3$) exposure on influenza prevalence reported that the cumulative RR (with 2–3 days of lag time) ranged from 0.94 (95% CI: 0.89, 1.00) to 1.26 (95% CI: 1.23, 1.29) among 47 cities in China (Chen et al., 2017). In another study investigating the association between acute upper respiratory infections and NO$_2$ (with the first quartile as reference) exposure, the cumulative RR (with 6 days of lag time) was estimated to be 1.25 (95% CI: 1.21–1.29) (Lin et al., 2013). In addition, the RR was 1.26 (95% CI:...
1.23.1.29) for pediatric influenza and O₃ (moving average of 10 days) exposure (Xu et al., 2013).

Fig. 5a illustrates the nonlinear relationships between the NO₂ exposure levels and RR at five specific lag days, which cumulatively represent the lag-exposure-outcome effects. The RR is higher on current-exposure levels and RR at five specific lag days, which cumulatively increase from 1.23 to 1.29 for pediatric influenza and O₃ exposures.

In general, the shorter the lag time and the higher the NO₂ exposure, the more obvious the health consequences of human exposure. This result suggests that the impact of NO₂ exposure on influenza is often acute, which is consistent with the previous research (Jhuang et al., 2016; Qu et al., 2019). Simultaneously, the latent effect of influenza virus is also worth noting. It should be noted that if someone who have been infected with virus or patients with only mild influenza symptoms but do not visit the hospital, these unaccounted discrete points will not be captured by the hospital reporting system, which introduces errors (Chen et al., 2017; Feng et al., 2016).

3.4. Attributable risk

According to the modeling results, the AF and AN due to the excessive NO₂ exposure are 14.01% (95% CI: 10.69–17.08%) and 2101 (95% CI: 1602–2561), respectively. Compared with commonly used ratio measures for summarizing the association (e.g., RR and odds ratio), AF and AN provided the information on the actual impact of NO₂ exposure on influenza (Rothman et al., 2008). Table 2 shows the estimated AF and AN of influenza due to NO₂ exposure exceeding the WHO air quality guideline of 40 μg/m³ over the seven-day lag. The health outcomes of air pollution exposure are generally illustrated from two perspectives. From a backward perspective, the AN is 2101 (95% CI: 1602–2561), and the AF is 14.01% (95% CI: 10.69–17.08%). From a forward perspective, the AN is 1902 (95% CI: 1445–2314), and the AF is 12.68% (95% CI: 9.75–15.62%). As the influenza cases beyond the study period are unable to be accurately accounted from the forward perspective, the AN and AF tend to be underestimated (Gasparini and Leone, 2014). Therefore, backward perspective is usually used when describing attributable risk.

It should be noted that even though there is a reasonable mechanism for a causal link between NO₂ and the flu infection, the reasons for other factors are not ruled out (Burnett et al., 2014; Tamerius et al., 2011). NO₂ pollution may be indicators of the real factor which cause influenza virus infection rather than posing direct risks to influenza (Burnett et al., 2014). Various factors such as individual characteristics, viral infectivity, treatment measures, and the interactive effects of various factors on influenza should be considered in further study (Lim et al., 2012). The previous studies found that women and the elderly were more sensitive to the environment because of physiological factors and relatively vulnerable immune system (Chai et al., 2020; Tian et al., 2017; Wang et al., 2013). Unfortunately, we were unable to include the basic and susceptible factors (e.g., age and sex) in the DLNM model due to the data unavailability.

4. Conclusions

We investigated the impact of NO₂ exposure on influenza prevalence in Chongqing, China during 2013–2017 using DLNM model. To the best of our knowledge, this is the first investigation on the attributable risk of influenza due to NO₂ exposure in densely populated mountainous regions with high humidity. We found that influenza prevalence is positively correlated with NO₂ with an RR of 1.24 (95% CI: 1.17–1.31) for every 10 μg/m³ increase in NO₂ exposure over a seven-day lag.

### Table 2

| Attributable Risk | Backward Perspective | Forward Perspective |
|-------------------|----------------------|---------------------|
| AF (% 95% CI)     | 14.01 (10.69, 17.08) | 12.68 (9.75, 15.62) |
| AN (cases, 95% CI)| 2101 (1602, 2561)   | 1902 (1445, 2314)   |

AN: attributable number; AF: attributable fraction; CI: confidence interval.

Approximately 14% of influenza cases were attributable by excessive NO₂ exposure. More epidemiological and mechanistic studies are needed to explore the relation between air pollution exposure and influenza for the development of public health policy and intervention.

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### Declaration of competing interest

The authors have no conflict of interest to disclose.

### CRediT authorship contribution statement

**Wen Zeng:** Writing - original draft, Visualization, Formal analysis.

**Han Zhao:** Writing - original draft, Data curation, Methodology.

**Rui Liu:** Investigation, Resources, Validation, Data curation.

**Wei Yan:** Project administration.

**Yang Qiu:** Conceptualization, Writing - review & editing.

**Fumo Yang:** Supervision, Funding acquisition, Writing - review & editing.

**Chang Shu:** Conceptualization, Writing - review & editing, Data curation.

**Yu Zhan:** Conceptualization, Supervision, Data curation, Writing - review & editing, Funding acquisition.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.109926.

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