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The impact of ambient fine particles on influenza transmission and the modification effects of temperature in China: A multi-city study

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Abstract

Background: There is good evidence that air pollution is a risk factor for adverse respiratory and vascular health outcomes. However, data are limited as to whether ambient fine particles contribute to the transmission of influenza and if so, how the association is modified by weather conditions.

Objectives: We examined the relationship between ambient PM2.5 and influenza incidence at the national level in China and explored the associations at different temperatures.

Methods: Daily data on concentrations of particulate matter with aerodynamic diameter < 2.5 μm (PM2.5) and influenza incidence counts were collected in 47 Chinese cities. A Poisson regression model was used to estimate the city-specific PM2.5–influenza association, after controlling for potential confounders. Then, a random-effect meta-analysis was used to pool the effects at national level. In addition, stratified analyses were performed to examine modification effects of ambient temperature.

Results: For single lag models, the highest effect of ambient PM2.5 on influenza incidence appeared at lag day 2, with relative risk (RR) of 1.015 (95% confidence interval [CI]: 1.004, 1.025) associated with a 10 μg/m3 increase in PM2.5. For moving average lag models, the significant association was found at lag 2–3 days, with RR of 1.020 (95% CI: 1.006, 1.034). The RR of influenza transmission associated with PM2.5 was higher for cold compared with hot days. Overall, 10.7% of incident influenza cases may result from exposure to ambient PM2.5.

Conclusions: Ambient PM2.5 may increase the risk of exposure to influenza in China especially on cooler days. Control measures to reduce PM2.5 concentrations could potentially also be of benefit in lowering the risk of exposure and subsequent transmission of influenza in China.

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1. Introduction

Coinciding with China’s rapid economic development and urbanization, air pollution has become a severe problem, and poses a major threat to the health of the Chinese population. Recent estimates suggest that annually air pollution in China kills > 1.5 million people each year, about 17% of the nation’s annual deaths (Rohde and Muller, 2015). One component of air pollution, in particular, is of increasing concern to public health experts; compared to other components, ambient particulate matter with aerodynamic diameter < 2.5 μm (PM2.5) is able to penetrate deep into the lung and into the circulatory system (S Feng et al., 2016). Exposure to PM2.5 is associated with a wide range of diseases including cardiovascular and respiratory disease (Arnold, 2014). In 2013, the Global Burden of Disease group estimated that exposure to ambient PM2.5 to be the 12th leading risk factor for the global burden of disease and responsible for 2.9 million deaths and 69.7 million disability-adjusted life-years, worldwide (Forouzanfar et al., 2015).

Despite substantial reductions in the burden of communicable disease in China over the past two decades, it remains a leading cause of death in the country (Wang et al., 2008). Of particular concern, both nationally and globally, is the increasing threat posed by emerging infectious diseases (e.g., severe acute respiratory syndrome [SARS] and the highly pathogenic avian influenza [H5N1]) in the Chinese population, both of which pose a significant public health threat (Wang et al., 2008). Few studies have examined the possible effect of ambient PM2.5 concentrations on risk of communicable disease in China, but those that have reported a positive association between ambient...
PM$_{2.5}$ and localised transmission of influenza (C. Feng et al., 2016; Huang et al., 2016; Liang et al., 2014). However, until now there has been no large-scale examination of the association due to past unavailability of PM$_{2.5}$ data and incident cases of influenza at the national level. Neither has there been any detailed exploration of the possible effect of temperature on the transmissibility by ambient PM$_{2.5}$ of the influenza virus. In this study, we collected daily data on ambient PM$_{2.5}$ levels, weather conditions and influenza incidence from 47 cities in China in order to reliably determine the association between PM$_{2.5}$ and influenza incidence and the potential modification effects of ambient temperature on the relationship.

2. Materials

2.1. Data collection

2.1.1. Influenza data

Daily data of influenza cases for 47 cities in China from September 9, 2013 to December 31, 2014 were obtained from the China Information System for Disease Control and Prevention (CISDCP). China has established a web-based notifiable infectious disease management system linked with health administrative datasets, the disease control institution and the medical and health institutions at five levels: township, county (district), prefecture, province and national (Wang et al., 2008). Influenza cases were defined according to Technical guides for prevention and control of influenza issued by China Ministry of Health (http://www.moh.gov.cn/zwgkzt/s9491/200802/38820.shtml): sudden onset of fever ≥38 °C, cough or sore throat, and absence of other diagnoses. As influenza is a notifiable disease (Class C), sentinel hospitals are required to collect nasopharyngeal swabs for each identified case which are subsequently sent to designated laboratories for virus isolation and further identification and results are submitted online within 24 h (Liang et al., 2014; Shu et al., 2010).

2.1.2. Ground PM$_{2.5}$ measurements

Ambient PM$_{2.5}$ concentrations were measured during the same time period as influenza data at 76 stations (Fig. S1 in Appendix) of the China Atmosphere Watch Network (CAWNET) administered by the China Meteorological Administration in 47 cities. Hourly PM$_{2.5}$ concentrations were measured using GRIMM EDM 180 environmental dust monitors. Further details regarding methods of measurements and the monitoring instruments used have been previously reported (Wang et al., 2015). To link PM$_{2.5}$ data with daily influenza case data, hourly PM$_{2.5}$ concentrations ($C_{\text{hour}}$) were converted to daily PM$_{2.5}$ concentrations ($C_{\text{daily}} = \sum_{1}^{24} C_{\text{hour}}/24$). City-level average concentrations were calculated if there were two or more stations in one city.

2.1.3. Meteorological data

Daily meteorological data were obtained from the China Meteorological Data sharing service system of the China Meteorological Administration (http://data.cma.gov.cn). Daily temperature, relative humidity, atmospheric pressure, wind speed, and hours of sunshine, were collected from 70 weather stations in 47 cities during the same period as the data for PM$_{2.5}$ and influenza incidence. The average value for each meteorological variable was calculated if there were two or more weather stations within a city.

2.2. Statistical analysis

The PM$_{2.5}$–influenza association was assessed using a two-stage analytic approach which has been widely applied in previous studies (Gasparini, Armstrong, and Kenward, 2012; Gasparini et al., 2015; Guo et al., 2014). In the first stage, the city-specific PM$_{2.5}$–influenza association was examined and in the second stage, a random effect meta-analysis was used to pool the associations at the country level.

2.2.1. First stage of analysis (city-specific associations)

A time series Poisson regression model was used to examine city-specific estimates allowing for over-dispersed case counts. Seasonality was controlled for using a natural cubic spline with seven degrees of freedom for freedom per year. A categorical variable was used to control for the confounding effect of day of the week. As weather conditions are associated with health outcomes and the impact can last for several days (Guo, Barnett, Pan, Yu, and Tong, 2011; Peng, Dominici, and Louis, 2006), we controlled for the potential confounding effects of five meteorological variables (daily mean temperature, relative humidity, air pressure, wind speed, and hours of sunshine) with moving average of the current day and the previous seven days using a natural cubic spline with three degrees of freedom for each of parameters (Guo et al., 2013).

To understand the characteristics of the lag associations between PM$_{2.5}$ and incident influenza, the associations were examined using a single lag model (from lag 0 to lag 7), and moving average lag model, separately. The city-specific effect estimates of influenza associated with a 10 µg/m$^3$ increase in PM$_{2.5}$ were calculated. To examine whether ambient temperature modified the associations between PM$_{2.5}$ and influenza, a stratified analysis was conducted according to daily temperature (for cold days, moderate cold days, moderate hot days, and hot days), by including an interactive term between PM$_{2.5}$ and temperature levels (as a categorical variable) in the city-specific regression model. The cold days, moderate cold days, moderate hot days, and hot days were classified by the quartile of 0–7 days’ moving average of temperature in each city during the study period. To further examine statistical significance of different effects of PM$_{2.5}$ for temperature subgroups, a meta-regression was conducted with the effect estimates of stratum-level analyses as dependent variable and categorical variable of daily temperature as dependent variable (Li et al., 2016).

2.2.2. Second stage of analysis

A meta-analysis was used to pool the city-specific effect estimates obtained from the first-stage model. The meta-analysis was fitted using a random effect model by maximum likelihood, to obtain the national pooled estimates for each lag type, respectively. The PM$_{2.5}$–influenza associations were expressed as the relative risk (RR) and 95% confidence interval (CI) of influenza associated with a 10 µg/m$^3$ increase in PM$_{2.5}$.

2.2.3. Computation of the population attributable fraction of influenza due to ambient PM$_{2.5}$

Considering the modified effects of ambient temperature on PM$_{2.5}$, incident influenza associations, the attributable fractions were calculated by pooled effect estimates ($\beta_j$) and PM$_{2.5}$ concentrations for each temperature strata according to the formulas reported by Evans et al. (2013). We used the following model to assess the daily influenza cases attributed to PM$_{2.5}$ for each city:

$$\text{A}_i = \text{Influenza}_i \times \left(1 - \frac{1}{\text{RR}_i} \right)$$

where $i$ is the day of the incident case of influenza; ‘A’ is the number of incident influenza cases attributed to PM$_{2.5}$ on day $i$; and ‘Influenza’ is the observed influenza cases on day $i$; the RR is calculated by exp.($\beta_i$) × moving average concentration of PM$_{2.5}$ on day $i$’s lag 1–2 days; $\beta$ is pooled effect estimate for different temperature stratum in corresponding to temperature on day $i$. 95% CI of pooled $\beta$ were used to calculate the 95% CI of attributable fraction with the above equation.

The overall population attributable fraction was assessed by dividing the sum of all city-specific attributable cases by the total number of incident cases. In addition, the attributable fractions were also calculated for each temperature stratum.

Sensitivity analyses were performed on the parameters for the city-specific model to test the robustness of our results. We varied the number of lag days to 15 days for meteorological variables, to examine
whether using seven lag days was sufficient to control for their effects on influenza. We modified the degrees of freedom for meteorological variables (3–6 df) and for time per year (6–10 df). To further test the robustness of results, multi-pollutant models were conducted by controlling for the effects of ambient NO2 and SO2. R software (version 3.2.2, R Development Core Team 2009) was used for all data analysis. The “mvmeta” package was used to fit the meta-analyses (Gasparrini et al., 2012).

3. Results

The spatial distribution of ambient PM2.5 concentrations between Chinese cities was geographically heterogeneous (Fig. 1). The highest levels of PM2.5 (>64.90 μg/m3) were generally located in cities in the western and northern regions of China and were more inland, in contrast to cities with low levels of PM2.5 (<33.50 μg/m3) which were located in the more southern, outer regions of China. Among the 47 cities, the city of Shijiazhuang in Hebei province had the highest PM2.5 concentration (98.14 μg/m3), while the lowest was recorded in the city of Xilingele in Inner Mongolia (11.90 μg/m3).

Overall, there were 76,902 incident cases of influenza cases during the time period of the study. The highest incidences of influenza occurred in cities including Beijing, Shanghai, Guangzhou and Chongqing, and the lowest incidences were observed in cities in the north eastern and central parts of China (Fig. 1). The highest daily count of new influenza (n = 32) was observed in Guangzhou city, Guangdong province whereas the lowest was in Xianning city, Hubei province. A summary of daily PM2.5 concentrations, incident influenza and the weather conditions for each city are shown in Table S1-S3 of the appendix.

Table 1 shows the correlations between ambient PM2.5 and the meteorological variables under investigation. PM2.5 concentrations were negatively correlated with temperature, relative humidity, wind speed and hours of sunshine significantly (r = −0.31 to −0.03, −0.25 and −0.12, respectively), but were positively correlated with atmospheric pressure significantly (r = 0.06). There was a strong correlation between relative humidity and hours of sunshine and weak correlations were observed between other meteorological factors.

Fig. 2 shows the pooled results from the meta-analysis for different single lag models (lag 0 to lag 7). The effect of PM2.5 on influenza was significant at lag days 2 and 3 (RR: 1.015 and 1.013; and 95% CI: 1.004, 1.025 and 1.003, 1.023, respectively). Thus, a moving average lag model at lag 2–3 days was performed to examine the cumulative effect across these two days.

Fig. 3 shows the effect of ambient PM2.5 on influenza at lag 2–3 days for each individual city and the overall pooled estimate at the national level. The effect estimates varied by city, with strong and significant effects observed in several cities in Southwest China and Central China including Guilin, Xianning, Kunming and Guangzhou. However, weak and insignificant effects were observed in cities located in Northeast China and South China including Shenyang, Changchun and Shenzhen. For the pooled estimate, the increased risk of influenza was significantly associated with an increase of 10 μg/m3 in PM2.5 at lag 2–3 days (RR: 1.020, 95% CI: 1.006, 1.034).

Fig. 4 shows the results for the stratified analyses by temperature levels per 10 μg/m3 increase in PM2.5 at lag day 2, lag day 3 and lag days’ 2–3. Significant associations at lag days’ 2–3 for cold days were observed (RR: 1.027, 95% CI: 1.010, 1.044), and a weaker, non-significant association was observed for hot days (RR: 0.982, 0.943, 1.023). For different lag types, the strongest effects were observed for cold days and the weakest effects for hot days. The effects on moderate cold and moderate hot days were similar.

Table 2 shows the number and fraction of incident influenza that might related to ambient lag days’ 2–3 PM2.5 moving average concentrations. Overall, approximately 10% of incident cases of influenza during the study period may result from exposure to ambient PM2.5 (PAF 10.72% [95% CI: 3.47%, 17.04%]). When stratified by temperature, the highest attributable fractions occurred on cold days (16.26, 95% CI: 6.67%, 24.53%). For moderate cold days and moderate hot days, the attributable fractions were similar. The effect of PM2.5 on incident influenza was stronger on cold days than hot days at lag 2–3 days (Table S4 in appendix).

Our findings were robust to a range of sensitivity analyses including increasing the number of lag days to 15 days for meteorological variables and when modifying the degrees of freedom for meteorological variables (3–6 df) and for time per year (6–10 df). Our findings remained robust after controlling for the effects of ambient SO2 and NO2 (Fig. S2 in the appendix).

4. Discussion

In recent years, public health experts have warned about the adverse acute and chronic health effects caused by severe haze and air pollution levels in China (Xu, Chen, and Ye, 2013). However few studies have focused on the possible association between pollution and communicable diseases. To our knowledge, this is the first study to examine the relationship between ambient PM2.5 and influenza incidence at the national level utilising PM2.5 monitoring data from 76 sites and influenza data obtained from surveillance systems from 47 cities throughout China. Our findings suggest that increased ambient PM2.5 concentrations are associated with incident case of influenza at lag days 2 and 3 and that the effect is most apparent at lag day 2 when using single lag models. There was also evidence of a negative interaction with temperature such that the association between PM2.5 and incident influenza was
stronger at cooler temperatures. Overall, assuming cause and effect, approximately one in every ten cases of incident influenza in China between September 2013 and December 2014 may result from exposure to ambient PM2.5.

Evidence for an association between ambient PM2.5 and the incidence of influenza at the national level is limited but our results are consistent with previous findings based on data from individual cities in China. One study conducted in Beijing reported that ambient PM2.5 concentrations were associated with the occurrence of influenza and that there was a time-lag effect (Liang et al., 2014). We observed that the lagged effects of PM2.5 on the incidence of influenza can be explained by the incubation period of the influenza virus consistent with previous studies (Lessler et al., 2009). A study from Beijing showed that the effects are strongest with a 2-day moving average of PM2.5, while another study from Nanjing reported that the strongest effects are for the current day and for the 2-day moving average (C Feng et al., 2016; Huang et al., 2016). The difference in lag days of PM2.5 may reflect the use of different methodologies and data sources.

There are plausible mechanisms for a causal association between PM2.5 and incident influenza although it is beyond the scope of this study to address this directly. For example, previous studies have examined the ability of fine particles to transmit viruses and have shown that fine particles which have the influenza virus attached, can accomplish long-range transportation under certain weather conditions such as dust storm days (Chen et al., 2010). Fine particles with viruses attached can also be inhaled resulting in the direct delivery of the viral agents to the respiratory epithelial cells (Chen et al., 2010; Jaspers et al., 2005). Other studies which have examined how PM2.5 exposure may impact on respiratory function and the inflammatory response, have reported that exposure to PM2.5 is associated with dysfunction of the pulmonary tracheal cilia and decreased activity of alveolar macrophages (Wong et al., 2009; Xing, Xu, Shi, and Lian, 2016) which in turn may enhance an individual's susceptibility to viral agents.

Although there are some underlying theories explaining the seasonal patterns of influenza, there has been no consideration given to the possible modifying role of air pollution on the association. Air pollution exhibits a similar seasonal variation to influenza outbreaks; for example, in winter, higher concentrations of PM2.5 have been reported possibly due to increased human activity and domestic heating leading to increased emissions (Kulshrestha, Satsangi, Masih, and Taneja, 2009). Several studies have reported that ambient temperature may modify the associations between air pollution and health (Kim, Lim, and Kim, 2015; Stafoggia et al., 2008), but whether this is also true for influenza has not been hitherto investigated. In our study, we observed stronger associations at cold temperatures, whereas there was no effect of high temperatures on the magnitude of the association between PM2.5 and incident influenza. These results are consistent with earlier findings including the results of an experimental study that indicated that most frequent viral

Table 1

| Factors         | PM2.5 | Temperature | Relative humidity | Atmospheric pressure | Wind speed | Hours of sunshine |
|-----------------|-------|-------------|-------------------|----------------------|------------|------------------|
| PM2.5           | 1.00  |             |                   |                      |            |                  |
| Temperature     | −0.31* | 1.00        |                   |                      |            |                  |
| Relative humidity| −0.03* | 0.28*        | −0.01             | 1.00                 |            |                  |
| Atmospheric pressure | 0.06*   | −0.11*      | −0.01             | 1.00                 | 1.00       |                  |
| Wind speed      | −0.25* | −0.06*      | −0.19*            | −0.05*               | −0.08*     | 0.06*            |
| Hours of sunshine| −0.12* | 0.07*        | −0.57*            | −0.05*               | −0.08*     | 1.00             |

* p < 0.01.

Fig. 2. Pooled relative risks (and 95% confidential intervals) of influenza incidence associated with an increase of 10 μg/m³ in PM2.5 at lag 0–7 days.
transmission occurred at 5 °C and was halted at 30 °C. It may be speculated that this reflects the inhibitory effect that cold air has on mucociliary clearance of the respiratory tract and greater viral stability in a low-temperature environment (Löwen, Mubareka, Steel, and Palese, 2007) both of which would enhance the transmissibility of the influenza virus. However, further studies are necessary before greater inference can be made.

Disease surveillance systems in China have substantially improved since the SARS epidemic in 2003. The CISDCP is now the world’s largest internet-based disease reporting system collecting real-time information about cases and virus subtypes and it provides essential and real-time information for policy makers (Wang et al., 2008). Influenza cases reported in the system were defined according to national criteria and identified by both routine clinical and laboratory examination. However, under-reporting of influenza cases may have occurred, as some individuals with influenza may not have attended hospital and therefore not been captured by the hospital reporting system (C Feng et al., 2016). Another limitation of the current study is that we did not have information on some demographic and behavioural factors – such as age, gender and cigarette smoking – which may be associated with incident influenza (Wang et al., 2016). However, the inability to include these covariates in the model is unlikely to have significantly confounded the association due to the lack of an association between these variables with PM$_{2.5}$.

Mortality and morbidity attributed to influenza has significant global health and economic consequences (WHO, 2015). Although most cases of influenza result in full recovery without serious complications, influenza contributes to the disease burden of communities and increases the risk of complications to the infection in the most vulnerable population subgroups (Livingston and Bernstein, 2015). As a part of an integrated strategy for infectious disease control and prevention, the potential effect of environmental factors on disease transmission and infection should be taken into consideration. Findings from this study suggest that ambient PM$_{2.5}$, particularly on cold days, increases the transmissibility of the influenza virus. Thus, following a period of heavy haze, preventive measures to prevent an increase in cases of influenza may be warranted both domestically and in neighbouring east Asian countries given the effect of emissions in China on surrounding countries (Kan, 2014).

Future studies that focused on other components of air pollution (e.g. NO) and environmental factors (e.g., meteorology, climate and
geography) are necessary to more fully understand the possible impact on infectious disease transmission (Ng and Gordon, 2015; Silva, Viana, Müller, Livi, and Dalcin, 2014). Studies are in need to establish the relationships between particle attachment and survival of influenza virus, and also methods should be developed to quantify airborne influenza virus and measure the concentration of influenza virus in ambient air especially for extremely low virus concentrations (Chen et al., 2010).

Competing financial interests

The authors declare they have no actual or potential competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2016.10.004.

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Table 2

Incident cases of influenza attributable to ambient PM2.5 at different temperatures.

|                      | Attributable number (95% CI) | Reported number | Attributable fraction (95% CI) |
|----------------------|-----------------------------|-----------------|-------------------------------|
| Cold days            | 6225 (2555, 9392)           | 38,293          | 16.26% (6.67%, 24.53%)        |
| Hot days             | 750 (41, 1378)              | 9428            | 7.95% (0.44%, 14.62%)         |
| All                  | 8240 (2669, 13,102)         | 76,902          | 10.72% (3.47%, 17.04%)        |

* We set the number of cases to zero on hot days due to there being no significant effect of PM2.5 on influenza incidence on hot days (see Fig. 4).

Fig. 4. Pooled relative risks and 95% confidential intervals of influenza incidence associated with an increase of 10 μg/m³ in PM2.5 at lag 2 day, lag 3 day, and moving average of lag 2–3 days, stratified by temperatures.
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