Effects of ambient PM$_1$ air pollution on daily emergency hospital visits in China: an epidemiological study

Gongbo Chen*, Sharshan Li*, Yongming Zhang, Wenyi Zhang, Daowei Li, Xuemei Wei, Yong He, Michelle L Bell, Gail Williams, Guy B Marks, Bin Jalaludin, Michael J Abramson, Yuming Guo

Summary

Background China is experiencing severe ambient air pollution. However, few studies anywhere have examined the health effects of PM$_1$ (particulate matter with aerodynamic diameter <1 µm), which are a major part of PM$_{2.5}$ (particulate matter with aerodynamic diameter <2.5 µm) and even potentially more harmful than PM$_{1.1}$. We aimed to estimate the effects of ambient daily PM$_1$ and PM$_{2.5}$ concentrations on emergency hospital visits in China.

Methods In this epidemiological study, we collected daily counts of emergency hospital visits from the 28 largest hospitals in 26 Chinese cities from Sept 9, 2013, to Dec 31, 2014. Ground-based monitoring data for PM$_1$ and PM$_{2.5}$ and meteorological data were also collected. Hospital-specific emergency hospital visits associated with PM$_1$ or PM$_{2.5}$ were evaluated with a time-series Poisson regression. The effect estimates were then pooled at the country level using a random-effects meta-analysis.

Findings The mean daily concentration of PM$_1$ in all cities was 42.5 µg/m$^3$ (SD 34.6) and of PM$_{2.5}$ was 51.9 µg/m$^3$ (41.5). The mean daily number of emergency hospital visits in all hospitals was 278 (SD 173). PM$_1$ and PM$_{2.5}$ concentrations were significantly associated with an increased risk of emergency hospital visits at lag 0–2 days (cumulative relative risk [RRs] 1.011 [95% CI 1.006–1.017] for a 10 µg/m$^3$ increase in PM$_1$ and 1.010 [1.005–1.016] for a 10 µg/m$^3$ increase in PM$_{2.5}$). Slightly higher RRs of ambient PM$_1$ and PM$_{2.5}$ pollution were noted among women and children than among men and adults, respectively, but without statistical significance. Given a cause-effect association, 4.47% (95% CI 2.05–6.79) and 5.05% (2.23–7.75) of daily emergency hospital visits in China could be attributed to ambient PM$_1$ and PM$_{2.5}$ pollution, respectively.

Interpretation Exposure to both ambient PM$_1$ and PM$_{2.5}$ were significantly associated with increased emergency hospital visits. The results suggest that most of the health effects of PM$_{2.5}$ come from PM$_1$.

Funding None.

Introduction

Ambient fine particulate matter (PM$_{2.5}$; particulate matter with aerodynamic diameter <2.5 µm) air pollution has been of increasing public concern and was estimated to cause 2.9 million deaths and 67.9 million disability-adjusted life-years (DALYs) in 2013 globally.

Particularly, ambient PM$_{2.5}$ contributes to a high burden of disease in east Asian countries including China. China is now experiencing exceptionally high levels of particulate matter air pollution, especially in densely populated cities. Numerous studies have confirmed associations between exposure to PM$_{2.5}$ and adverse health effects, including cardiovascular and respiratory diseases, neonatal conditions, and hospital admissions.

Current research interest in PM$_1$ (particulate matter with an aerodynamic diameter <1 µm), a major component of PM$_{2.5}$, is increasing. Previous studies have suggested that with a smaller particle size, PM$_1$ is more harmful than PM$_{2.5}$. This particulate is more likely to reach deeper into the respiratory system carrying with it more toxins from anthropogenic emissions. Ambient PM$_1$, contributed nearly 80% of PM$_{2.5}$ in most particulate matter observation stations in China.

Thus, understanding the spatial variations of ambient PM$_1$ and its effects on health are relevant to the prevention and control of air pollution in China. To date, few studies worldwide have focused on ambient PM$_1$, due to the unavailability of air monitoring data. Although a study of one city in China reported a stronger association of PM$_1$ with cardiovascular mortality than other constituents of ambient particulate pollution, no published studies have been done at the regional scale or at the national scale assessing effects of PM$_1$ on morbidity.

We aimed to estimate the effects of ambient daily PM$_1$ and PM$_{2.5}$ concentrations on emergency hospital visits in China.

Methods

Data collection

Daily counts of emergency hospital visits

In this epidemiological study, we collected daily counts of emergency hospital visits from Sept 9, 2013, to Dec 31, 2014,
Evidence before this study
PM1 (mass concentrations of particles with aerodynamic diameter <1 µm) is a major component of PM1–2·5 (<2·5 µm). Due to smaller particle size, PM1 is more harmful than PM2·5 because it reaches deeper into the respiratory system carrying with more toxins from anthropogenic emissions. Evidence for health effects of PM1 is very limited, because it is not routinely monitored in China or elsewhere in the world. We searched PUBMED, Web of Science, Google Scholar, and CNKI with the terms “mortality”, “morbidity”, “health”, “PM1”, and “China” in English and Chinese on Feb 2, 2017. As result, we identified only one study in Guangzhou, China, exploring the effects of PM1 on cardiovascular mortality. To date, no large scale study has investigated the health effects of PM1 at the country level in China and even worldwide.

Added value of this study
To the best of our knowledge, this is the first national study to examine the associations between exposures to ambient PM1 and PM2·5, and emergency hospital visits using data from 26 cities in China to calculate the attributable fractions due to PM1 and PM2·5. In this study, we collected daily data for emergency hospital visits from 28 largest hospitals in China, as well as daily measurements PM1 and PM2·5 from 26 cities where the hospitals were located. The associations between exposures to ambient PM1 and PM2·5, and emergency hospital visits were examined with a two-stage analytical approach and the population attributable fractions of emergency hospital visits due to daily concentrations PM1 and PM2·5 were calculated and compared.

Statistical analysis
Daily counts of emergency hospital visits for each hospital were linked with air pollution data from the nearest ground monitoring station for each of the 26 cities. The average distance from hospital to the nearest ground monitoring station was 6·4 km (SD 2·8; appendix p 1). A two-stage analysis strategy was developed to assess the effects of PM1, PM1–2·5, and PM2·5 on emergency hospital visits. Such a strategy has been widely used in environmental epidemiology. At the first stage, the relation between emergency hospital visits and PM1, PM1–2·5, or PM2·5 was assessed by Poisson regression. In stage 1, the hospital-specific model, emergency hospital visits associated with PM1, PM1–2·5, or PM2·5 were examined using a time-series Poisson regression model. The factors used in the analysis were shown:  

\[ \log(E_i) = \beta_0 + \beta_1 \times PM_{1i} + \beta_2 \times PM_{1–2.5i} + \beta_3 \times PM_{2–5i} + \beta_4 \times TEMP_i + \beta_5 \times AP_i + \beta_6 \times RH_i + \beta_7 \times WS_i + \beta_8 \times SH_i + \delta t_i \]  

where \( E_i \) is the daily count of emergency hospital visits for hospital i, and \( PM_{1i} \), \( PM_{1–2.5i} \), and \( PM_{2–5i} \) are the daily concentrations of PM1, PM1–2·5, and PM2·5, respectively. \( TEMP_i \), \( AP_i \), \( RH_i \), \( WS_i \), and \( SH_i \) are the daily average temperature, atmospheric pressure, wind speed, and hours of sunshine, respectively. \( \delta t_i \) is the daily time trend for hospital i.
where $E_{ij}$ is the expected count of emergency hospital visits in hospital $i$ on day $j$; $b_{5}(PM_{2.5})$ is the concentrations of PM$_{1}$, PM$_{1–2.5}$, or PM$_{2.5}$ in the city where hospital $i$ was located on day $j$ using a Constrained Distributed Lag Model with 3 degrees of freedom (df) natural cubic spline for lag day; $t_{i}$ is a variable for time with a natural cubic spline (7 df per year) on day $j$ to control for the long-term trend and seasonality; TEM, AP, RH, WS, SH are 7-day moving averages of daily mean temperature, atmospheric pressure, relative humidity, wind speed, and hours of sunshine, respectively, in the city where hospital $i$ was located on day $j$ with 3 df natural cubic splines; $dow_{i}$ is a categorical variable for day of week on day $j$. This model was fitted separately for each hospital and for each pollutant (PM$_{1}$, PM$_{1–2.5}$, and PM$_{2.5}$). In this stage of model, we set 7 as maximum lag day of PM because the significant effects of PM on emergency hospital visits during lags of 0–5 days were reported by previous studies. The residual deviance and autocorrelation were used to check the adequacy of the first stage of the model.

In stage 2, the meta-analysis, coefficients and corresponding covariance matrix of the first stage hospital-specific model were used in the second-stage analysis. A random-effects meta-analysis was conducted with maximum likelihood estimation to pool the hospital-specific results into an overall estimated effect that represented the national level effect. The lagged effects and cumulative effects of PM$_{1}$, PM$_{1–2.5}$, and PM$_{2.5}$ on emergency hospital visits were calculated and expressed as relative risks (RRs) and corresponding 95% CIs with a 10 µg/m$^3$ increase in PM$_{1}$, PM$_{1–2.5}$, or PM$_{2.5}$, respectively. The lagged effects of particulate matter on emergency hospital visits were firstly pooled, and then, cumulative effects were further examined for the lag days with significant associations. Because our initial analysis showed that the associations between PM$_{1–2.5}$ and emergency hospital visits were not significant at any lag day, we did not perform the meta-analysis for cumulative effects of PM$_{1–2.5}$, or calculate its attributable fraction.

Population fractions (PAFs) of emergency hospital visits attributed to PM$_{1}$ and PM$_{2.5}$ were calculated using previously published methods. The following formula was used:

$$AF_{ij} = 1 - \exp\left(-\sum_{k=0}^{K} \beta_{ij,k}\right)$$

$$AN_{ij} = n_{ij} \cdot AF_{ij}$$

where “$AF_{ij}$” indicates attributable fraction of emergency hospital visits due to PM$_{1}$ and PM$_{2.5}$ on day “$j$” in hospital “$i$”; “$K$” and “$K$” were lag day and maximum lag day, respectively; “$\beta_{ij,k}$” indicates the pooled effect estimate calculated with a backward approach for PM$_{1}$/PM$_{2.5}$ on day “$j$–$k$”; “$n_{ij}$” and “$AN_{ij}$” are reported number of emergency hospital visits and attributable number of emergency hospital visits to PM$_{1}$, or PM$_{2.5}$, on day “$j$” in hospital “$i$”, respectively. The attributable number of emergency hospital visits for each hospital were calculated and summed to get the total attributable numbers of emergency hospital visits at the national level (as represented by the 26 major cities), which were then divided by total counts of emergency hospital visits to obtain the pooled PAFs. The upper limit and lower limit of CIs for RRs were used to calculate the CIs for PAFs.

Sensitivity analyses were done to examine the robustness of the results. We developed multi-pollutant models, adding variable for daily concentrations of sulfur dioxide (SO$_{2}$) and nitrogen dioxide (NO$_{2}$), to check whether the estimated PM$_{1}$ and PM$_{2.5}$ associations for emergency hospital visits were modified by other air pollutants. We changed the maximum lag days from 7 to 15 for meteorological variable and modified the df of meteorological variables (3–6 df) and time of the year (6–10 df). We only controlled for ambient temperature and relative humidity to check if we over controlled the effects of weather conditions.

Data were analysed using R software (version 3.2.2, R Development Core Team 2009). The “mvmeta” package was used to fit the meta-analysis.

**Results**

The overall mean concentrations of daily PM$_{1}$ and PM$_{2.5}$ in the 26 cities were 42.5 µg/m$^3$ (SD 34.6) and 51.9 µg/m$^3$ (41.5), respectively. The highest concentrations of PM$_{1}$ and PM$_{2.5}$ were observed in winter (mean 61.4 µg/m$^3$ and 71.7 µg/m$^3$, respectively), whereas the lowest concentrations were observed in summer (mean 25.3 µg/m$^3$ and 31.6 µg/m$^3$, respectively). Average daily concentrations of PM$_{1}$ and PM$_{2.5}$ in the 26 cities during the study period are shown in figure 1. Highest concentrations of PM$_{1}$ (>60 µg/m$^3$) and PM$_{2.5}$ (>80 µg/m$^3$) were observed in southwestern and northern China (Chengdu, Xi’an, Beijing, and Taiyuan), whereas the lowest concentrations (PM$_{1}$ and PM$_{2.5}$ <30 µg/m$^3$) were observed in southern China (Haikou, Shenzhen, and Fujian). The ratio of PM$_{1}$:PM$_{2.5}$ in the 26 cities ranged from 0.67 to 0.97, and for most cities (18 of 26 cities), the PM$_{1}$:PM$_{2.5}$ ratios exceeded 0.8. The highest ratios (>0.95) occurred in Hefei, Changsha, and Chongqing, whereas the lowest ratios (<0.70) occurred in Hohhot, Lanzhou, and Nanjing. The mean daily number of emergency hospital visits in all hospitals was 278 (SD 173). Among the 28 hospitals included in this study, the Sino-Japanese Friendship Hospital in Beijing had the highest daily average number of emergency hospital visits (n=620) and Tongji Hospital in Wuhan had the lowest (n=59). A summary of emergency hospital visits for all hospitals is shown in the appendix (p 1).

The associations between air pollutants and meteorological variables during the study period are...
shown in the appendix (pp 2–3). Daily concentrations of PM₁ and PM₂·₅ were highly associated ($r=0.96$, $p<0.0001$). PM₁ and PM₂·₅ were negatively associated with ambient temperature, wind speed, and hours of sunshine (PM₁ and temperature, $r=-0.36$, $p<0.0001$; PM₂·₅ and wind speed, $r=-0.23$, $p<0.0001$; PM₁ and hours of sunshine: $r=-0.09$, $p<0.0001$). Weak associations were noted between PM₁ or PM₂·₅ and relative humidity and atmospheric pressure.

Pooled RRs for emergency hospital visits associated with a 10 µg/m³ increase in PM₁, PM₁–₂·₅, or PM₂·₅ during lag 0–7 days are shown in figure 2. Significant effects of PM₁ and PM₂·₅ were observed at lag 0, 1, and 2 days, with strongest effects at lag 0 day (RRs 1·005 [95% CIs 1·003–1·008] and 1·005 [1·002–1·007], respectively) and lowest effects at lag 2 days (RRs 1·002 [95% CI 1·001–1·004] and 1·002 [1·001– 1·004], respectively). Ambient PM₁ had similar effects on emergency hospital visits as PM₂·₅. No significant association between PM₁–₂·₅ and emergency hospital visits was observed for any lag day. Thus, we did not perform the meta-analysis for cumulative effects of PM₁–₂·₅ or calculate its attributable fraction in the following analyses.

Because significant emergency hospital visits associated with PM₁ and PM₂·₅ were observed at lag 0–2 days, their cumulative effects were further examined. Hospital-specific and pooled cumulative effects of PM₁ or PM₂·₅ on emergency hospital visits at lag 0–2 days are shown in figure 3. PM₁ and PM₂·₅ significantly increased the risk of emergency hospital visits.
visits at lag 0–2 days (cumulative RR 1·011 [95% CI 1·006–1·017] and 1·010 [1·005–1·016], respectively). For individual cities, the highest RRs of PM1 and PM2·5 were observed in hospitals in Shanghai, Shenzhen, and Guangzhou, while the lowest RRs were observed in hospitals in Taiyuan and Urumqi. Stratified analyses by sex and age group showed that the RRs of emergency hospital visits for PM1 and PM2·5 were slightly higher among women and children aged 14 years and younger than among men and adults, respectively (figure 4), although the results were not statistically different. Stratified analyses by clinic department showed that there were strong and significant effects of PM1 and PM2·5 on department of internal medicine and pediatrics, while no significant effects were observed for other clinic departments (table 1).

Overall, 4·47% (95% CI 2·05–6·79) of observed emergency hospital visits during the study period could be attributed to estimated effects of PM1 at lag 0–2 days and 5·05% (2·23–7·75) could be attributed to PM2·5 (table 2). Sensitivity analyses showed that PM1 and PM2·5 were still significantly associated with increased emergency hospital visits at lag 0–2 days (cumulative effects) after controlling for ambient SO2 and NO2 (appendix p 4). Furthermore, including 7–15 lag days for meteorological variables, using 3 df for meteorological variables and 6–10 df per year for time, did not substantially alter the effect estimates of the associations between PM1 or PM2·5 and emergency hospital visits. Only controlling for ambient temperature and relative humidity did not change the results (appendix p 5).

Discussion

In this study, we examined the effects of PM1 on emergency hospital visits in China, and compared the effects of PM1 and PM2·5 on emergency hospital visits in the country. In
Articles

Figure 4: Pooled relative risks of emergency hospital visits associated with a 10 μg/m³ increase in PM₁ and PM₂·₅ at lag 0–2 days stratified by sex and age groups
Error bars are 95% CIs. PM₁=particulate matter with aerodynamic diameter less than 1 μm. PM₂·₅=particulate matter with aerodynamic diameter less than 2·₅ μm.

Table 1: Relative risks (95% CIs) of emergency health visits associated a 10 μg/m³ increase in ambient PM₁ or PM₂·₅ at lag 0–2 days, stratified by clinic department

<table>
<thead>
<tr>
<th>pollutant</th>
<th>internal medicine</th>
<th>Paediatrics</th>
<th>Obstetrics and gynecology</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM₁</td>
<td>1·012 (1·006–1·017)</td>
<td>1·016 (1·002–1·031)</td>
<td>0·996 (0·986–1·007)</td>
<td>1·000 (0·990–1·010)</td>
</tr>
<tr>
<td>PM₂·₅</td>
<td>1·011 (1·005–1·016)</td>
<td>1·015 (1·002–1·028)</td>
<td>0·997 (0·989–1·005)</td>
<td>1·000 (0·991–1·009)</td>
</tr>
</tbody>
</table>

Table 2: Population fraction of emergency health visits attributed to ambient PM₁ and PM₂·₅

<table>
<thead>
<tr>
<th>Attributable number of emergency health visits (95% CI)</th>
<th>Observed total emergency health visits</th>
<th>Attributable fraction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM₁: 145 704 (66 989–221 459)</td>
<td>3 260 001</td>
<td>4.47% (2.05–6.79)</td>
</tr>
<tr>
<td>PM₂·₅: 164 584 (72 653–252 514)</td>
<td>3 260 001</td>
<td>5.05% (2.23–7.75)</td>
</tr>
</tbody>
</table>

PM₁=particulate matter with aerodynamic diameter less than 1 μm. PM₂·₅=particulate matter with aerodynamic diameter less than 2·₅ μm.

No international or domestic study in China has been done at a country level that has focused on the health effects of PM₁. Our findings are consistent with the study by Lin and colleagues² from Guangzhou, China, which reported significant association of lagged PM₁ and cardiovascular mortality and further reported that PM₁ was more closely associated with cardiovascular mortality with higher effects than PM₂·₅, or particulate matter with aerodynamic diameter less than 10 μm (PM₁₀). Health effects associated with ambient particulate matter have been reported by numerous previous studies.²⁴,²⁷ However, most of them focused on PM₂·₅ and PM₁₀; far less scientific evidence exists for the health effects of smaller particles, including PM₁ and ultrafine particles. Existing research indicates that particle size is an important determinant of adverse health effects.²⁸ Smaller particles, especially PM₁ and ultrafine particles that can more easily reach the acinar part of the respiratory tract, are more likely to persist in the lung parenchyma, and have higher surface-to-volume ratios, thereby promoting oxidative stress and inflammation.²⁹ PM₁ might also contain more toxins from anthropogenic emissions, including metals, which are able to cause further lung injury and even lead to gene damage and cancer.³⁰ In addition, airborne bacteria associated with urban particulate matter might be linked with some respiratory diseases, including asthma.³¹,³² The chemical composition of particles can differ by the size of the particles in relation to the various processes and sources that form them, which could contribute to different health responses.³³ Children’s vulnerability to particulate matter air pollution might be due to their weaker ability to regulate pro-inflammatory and anti-inflammatory mediators.³⁴ Different health effects by sex could be associated with a range of socioeconomic, behavioural, and psychological factors.³⁵ For instance, women have smaller lungs and airway diameters than do men, which might increase airway reactivity and exacerbate particulate deposition.³⁶ Higher prevalence of mental conditions, such as frequent mental distress, was observed among older women aged 65 or older than among men aged 65 or older.³⁷ A study from California, USA, women also tend to spend more time outside than men because they are less likely to get full time jobs.³⁸ We did not find higher RRs for emergency hospital visits in individuals aged 65 years and older, which is not consistent with previous studies.³⁹ The reason might be related to their potential barriers to get access to health-care services in China.⁴⁰ Source apportionment studies indicated that a much higher proportion of PM₁ originated from combustion (eg, biomass fuel burning) compared with PM₂·₅, although the major components had the same sources. In our study, PM₁ contributed more than 80% of ambient PM₂·₅, which is a higher ratio than those reported in other countries.³⁴,⁴³ This might be due to the rapid industrial development and increased energy demand in China, especially in the mega cities with rapid population and industrial growth.⁴⁴
We also found that PM₁ had similar short-term effects on emergency hospital visits as did PM₂·₅ and the attributable fraction due to PM₁ approached that of PM₂·₅. From this finding we could infer that most of the adverse effects of PM₁ on health in China as reported by previous studies could be attributed to PM₂·₅. Particularly, there were no significant associations between PM₁–₂·₅ and emergency hospital visits. Other studies have also suggested the important role of smaller particles in ambient particulate matter pollution. A study in Shenyang, China, reported that particles smaller than 0·5 µm were most strongly associated with daily mortality, while in Beijing, ultrafine particles have been shown to have strongest effects on daily emergency hospital visits for cardiovascular disease. Although health effects of PM₁ have been documented by numerous studies, evidence to date for adverse health effects of smaller particles is very limited and even existing epidemiological evidence is inconsistent. The physiological and biological mechanisms linking PM₁ with mortality, morbidity, and specific diseases should be further explored by future studies.

There was heterogeneity in emergency hospital visits associated with PM₁, PM₂·₅, and lag structure (figure 3; appendix pp 6–7). This could be associated with different exposure levels of PM₁ and PM₂·₅ ratios as well as particulate matter components in different cities. The heterogeneity might also be related to social and environmental factors, including economic development, age structure, and land-cover characteristics. PM₁ and larger particles originate from different sources. PM₁ is mainly created through either combustion of fuels or the process of air particle formation, while coarse particles are mainly formed through mechanical processes, such as dust carried by wind and loose soil. PM₂·₅ can be created by both of these two processes. The Chinese Government published national ambient air quality standards (NAAQS) in 2012 but no standard was set for PM₁. In fact, PM₁ is not regulated in many other countries, such as in the USA, due to the lack of scientific evidence on this pollutant. In the future, more studies are in need to explore the spatial and temporal patterns of PM₁ and to evaluate its associations with short-term and long-term health outcomes. These studies will also provide valuable information and evidence for policy makers when promulgating standards and guidelines for the control of PM₁ pollution both in China and other countries. As indicated by our study, high concentrations of ambient PM₁ were associated with significantly increased daily emergency hospital visits and continuing high emergency hospital visits in the following 2 days. This information will assist hospital administrators in their allocation of resources to manage the potential increase in emergency hospital visits during and following severe hazy weather, like the widespread dense haze that occurred in China in January, 2013.

To the best of our knowledge, this is the first large-scale study in China, and even worldwide, assessing the acute effects of ambient PM₁ on emergency hospital visits and comparing its effects to PM₂·₅, based on health data and air pollution data in 26 cities. The use of constrained distributed lag models provided flexibility in assessing the exposure-lag-response relation between air pollution and emergency hospital visits, after controlling for potential confounders. Our results were robust in a series of sensitivity analyses. However, there were several limitations to our study. We used particulate matter data from fixed monitoring sites in each city to link with health data rather than individual exposure, which could cause measurement errors in exposure assessment. However, such measurement error leads the effect estimates to null. This means that if we had individual exposure data, our effect estimates for PM₁ and PM₂·₅ would have been higher than our current results. We could not put all air pollutants in the same model considering the strong colinearity between air pollutants caused by the commonality of sources or photochemical interactions. We did not assess the associations between PM₁ or PM₂·₅ and cause-specific emergency hospital visits, because the final diagnosis of all emergency hospital visits were not available. Finally, study cities were not evenly distributed in China with less cities in western China due to less developed economy and smaller population. Future research should include available data for these factors in the analyses.

In this study, we found exposure to ambient PM₁ and PM₂·₅ were significantly associated with increased emergency hospital visits and effects of PM₁ were similar to those from PM₂·₅. Most emergency hospital visits attributed to PM₂·₅ were from PM₁. To effectively control particulate matter pollution in China, evidence-based air quality standards and guidelines for PM₁ should be developed in the near future.

Contributors YG designed and supervised the study. GC analysed the data and wrote the paper. YZ, WZ, DL, XW, and YH prepared the database and conducted the quality assurance. SL, MLB, GW, GBM, BJ, and MJA reviewed and edited the report.

Declaration of interests We declare no competing interests.

Acknowledgments YG was supported by the Career Development Fellowship of Australian National Health and Medical Research Council (#APP1107107). SL was supported by the Early Career Fellowship of Australian National Health and Medical Research Council (#APP1109193) and Seed Funding from the National Health and Medical Research Council (NHMRC) Centre of Research Excellence (CRE)—Centre for Air Quality and health Research and evaluation (CAR) (APP1030529). GC was supported by China Scholarship Council (CSC). We thank the following hospitals that provided data for hospital emergency visits: The second Xiangya Hospital of Central South University, Changsha, Hunan; First Affiliated Hospital of Jilin University, Changchun, Jilin; Xinqiao Hospital, Chongqing; Zongshang Hospital of Xiamen University, Xiamen, Fujian; Inner Mongolia Autonomous Region People’s Hospital, Hohhot, Inner Mongolia; Affiliated Hospital of Guilin Medical College, Guilin, Guangxi; Zunyi Medical College Hospital, Zunyi, Guizhou; Affiliated Hospital of Chengde Medical College, Chengde, Hebei; Affiliated Hospital of Qinghai...
University, Xining, Qinghai; Anhui Provincial Hospital, Hefei, Anhui; Hainan Provincial People’s Hospital, Haikou, Hainan; First Hospital of Shanxi Medical University, Taiyuan, Shanxi; Tongji Hospital, Xian, Shaanxi; First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning; PLA General Hospital of Lanzhou Military Region, Lanzhou, Gansu; Haile Hospital, Tianjin; Tongji Hospital, Huazhong University of Science and Technology, Wuhan, Hubei; West China Hospital, Sichuan University, Chengdu, Sichuan; Zhongshan Hospital of Fudan University, Shanghai; PLA General Hospital of Nanjing Military Region, Nanjing, Jiangsu; First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian; First Affiliated Hospital of Soochow University, Suzhou, Jiangsu; Nanfang Hospital, Southern Medical University, Fuzhou, Fujian; First Affiliated Hospital of Soochow University, Suzhou, Jiangsu; Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong; Qindao Municipal Hospital, Qingdao, Shandong; First Affiliated Hospital of Guangzhou Medical University, Nanning, Guangxi; Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, Zhejiang; Shenzhen People’s Hospital, Shenzhen, Guangdong; and First Affiliated Hospital of Baotou Medical College, Baotou, Inner Mongolia.

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