Associations between daily air quality and hospitalisations for acute exacerbation of chronic obstructive pulmonary disease in Beijing, 2013–17: an ecological analysis

Lirong Liang*, Yutong Cai*, Benjamin Barratt, Baolei Lyu, Queenie Chan, Anna L Hansell, Wuxiang Xie, Di Zhang, Frank J Kelly, Zhaohui Tong

Summary
Background Air pollution in Beijing has been improving through implementation of the Air Pollution Prevention and Control Action Plan (2013–17), but its implications for respiratory morbidity have not been directly investigated. We aimed to assess the potential effects of air-quality improvements on respiratory health by investigating the number of cases of acute exacerbations of chronic obstructive pulmonary disease (COPD) advanced by air pollution each year.

Methods Daily city-wide concentrations of PM\textsubscript{2.5}, PM\textsubscript{10}, PM\textsubscript{coarse} (particulate matter >2.5–10 µm diameter), nitrogen dioxide (NO\textsubscript{2}), sulphur dioxide (SO\textsubscript{2}), carbon monoxide (CO), and ozone (O\textsubscript{3}) in 2013–17 were averaged from 35 monitoring stations across Beijing. A generalised additive Poisson time-series model was applied to estimate the relative risks (RRs) and 95% CIs for hospitalisation for acute exacerbation of COPD associated with pollutant concentrations.

Findings From Jan 18, 2013, to Dec 31, 2017, 161 613 hospitalisations for acute exacerbation of COPD were recorded. Mean ambient concentrations of SO\textsubscript{2} decreased by 68% and PM\textsubscript{2.5} decreased by 33% over this 5-year period. For each IQR increase in pollutant concentration, RRs for same-day hospitalisation for acute exacerbation of COPD were 1.029 (95% CI 1.023–1.035) for PM\textsubscript{10}, 1.028 (1.021–1.034) for PM\textsubscript{2.5}, 1.018 (1.013–1.022) for PM\textsubscript{coarse}, 1.036 (1.028–1.044) for NO\textsubscript{2}, 1.019 (1.013–1.024) for SO\textsubscript{2}, 1.024 (1.018–1.029) for CO, and 1.027 (1.010–1.044) for O\textsubscript{3} in the warm season (May to October). Women and patients aged 65 years or older were more susceptible to the effects of these pollutants on hospitalisation risk than were men and patients younger than 65 years. In 2013, there were 12 679 acute exacerbations of COPD cases that were advanced by PM\textsubscript{2.5}, pollution above the expected number of cases if daily PM\textsubscript{2.5} concentrations had not exceeded the WHO target (25 µg/m\textsuperscript{3}), whereas the respective figure in 2017 was 7 377 cases.

Interpretation Despite improvement in overall air quality, increased acute air pollution episodes were significantly associated with increased hospitalisations for acute exacerbations of COPD in Beijing. Stringent air pollution control policies are important and effective for reducing COPD morbidity, and long-term multidimensional policies to safeguard public health are indicated.

Funding UK Medical Research Council.

Introduction Chronic obstructive pulmonary disease (COPD) is a leading contributor to disease burden globally.1 A survey in China2 showed an estimated nationwide prevalence of spirometry-defined COPD of 13·7% among people aged 40 years and older in 2012–15, a 5·5% increase from the 2002–04 survey, and suggested ambient air pollution resulting from rapid urbanisation as a probable contributor to this emerging COPD epidemic.

Although ambient air pollution might contribute to a more rapid decline of lung function and subsequent onset of COPD in adults,14 its adverse effects on patients with existing COPD have also been widely reported. Short-term exposure to air pollution has been positively associated with COPD-related emergency department visits, hospital admissions, and mortality.15 However, not all of these studies have specifically focused on acute exacerbations of COPD, an outcome that is often associated with COPD progression and prognosis, repeated access to health care, impaired quality of life, and mortality. A systematic review of 46 studies on acute exacerbations of COPD published until 2015 revealed heterogeneous evidence across studies in geographically diverse regions, but included few epidemiological studies from regions with severe ambient air pollution. Increasing numbers of studies have been reported from such regions in the past 4 years regarding short-term and long-term associations between air pollution and respiratory morbidity and mortality to help strengthen the evidence base.15,17,18 Additionally, from both clinical and policy perspectives, important knowledge gaps remain concerning the exposure–response relationships between extremely high concentrations of ambient air pollution and risk of hospitalisation for acute exacerbation of COPD.
In 2013, China launched the Air Pollution Prevention and Control Action Plan (APPCAP), in which various stringent measures (appendix p 3) were implemented nationwide to curb air pollution, particularly from industrial sectors, to interim targets by the end of 2017. Beijing and the surrounding areas were among the most stringently targeted regions. During this 5-year period, concentrations of sulphur dioxide (SO₂) were reduced by 70% and fine particulate matter (PM) by 33%. This progress provides an opportunity to study the potential health gains of this milestone policy.

In the current study, we investigated the associations between daily average concentrations of criteria air pollutants and daily hospitalisations for acute exacerbations of COPD in 2013–17 in Beijing. On the basis of the observed effect estimates, we calculated the number of cases of acute exacerbations of COPD advanced by air pollution each year to assess the potential effects of the recorded air-quality improvements.

**Methods**

**Study setting and exposure data**

Since 2013, PM₁₀ (µg/m³), PM₂·₅ (µg/m³), SO₂ (µg/m³), nitrogen dioxide (NO₂; µg/m³), carbon monoxide (CO; mg/m³) and ozone (O₃; µg/m³) have been routinely measured at 35 monitoring stations spread throughout Beijing (appendix p 2). The monitoring network is run by the Beijing Environmental Protection Bureau in accordance with the new Chinese national standard (GB 3095-2012). The monitoring stations were strategically assigned in representative locations to monitor emission sources from vehicles (road site, n=5), urban anthropogenic activities (urban site, n=23), natural activities (rural site, n=1), and regional transport or background (regional site on the outskirts of Greater Beijing, n=6). At each station, for each pollutant except O₃, hourly data are usually available for at least 20 h each day to calculate the daily 24-h average (mean) concentration. For O₃, hourly data should be available for at least 6 h in every 8 h to calculate a daily maximum 8-h moving average concentration.

A daily city-wide mean concentration for each pollutant, based on the daily mean readings from all these 35 stations, is reported on the Environmental Protection Bureau air-quality reporting platform. We obtained these daily city-wide average data from Jan 18, 2013, to Dec 31, 2017 (1809 days), and the quality check was satisfied (appendix p 4). Daily meteorological data (daily mean temperature [°C] and relative humidity [%]) were collected from the Beijing Meteorological Service website.
Of the 1809 days, there were 5 days with a missing city-wide daily average for all pollutants, which were excluded from the analysis. In the remaining 1804 days, a city-wide daily average was available for all pollutants, except 5 days of missing data and 97 days of distorted data for daily city-wide average PM$_{10}$ (appendix p 4), and 34 days of missing daily city-wide average O$_3$. To reconstruct the missing or distorted PM$_{10}$ data for those 102 days, we used 24-h average concentrations for PM$_{10}$ on the same date multiplied by the ratio between annual mean concentration for PM$_{10}$ and annual mean concentration for PM$_{2·5}$, derived for that year. The annual ratios derived were 1·312 for 2013, 1·444 for 2014, 1·441 for 2015, 1·379 for 2016, and 1·631 for 2017, which were similar to previously reported results. We did not reconstruct data for O$_3$ because of the complex formation mechanism of this pollutant. Therefore, our analyses of PM$_{10}$, PM$_{2·5}$, PM$_{1·0}$ (defined as PM $>$2·5–10 μm in diameter), SO$_2$, NO$_x$, and CO were based on the 1804-day dataset, and the analyses of O$_3$ were based on a 1770-day dataset.

This study was approved by the Research Ethics Board of Beijing Chaoyang Hospital (approval number 2018-ke-303).

**Hospital data**

Daily counts of hospital admissions for acute exacerbation of COPD were obtained from a hospital discharge database operated by Beijing Public Health Information Centre. In Beijing, each government and private hospital at secondary or tertiary level is required to submit their discharge records to the database. A three-tier health-care system is operated in China, where secondary and tertiary level hospitals are general hospitals eligible to provide specialised care. Each record includes data on age, sex, residential address, admitting hospital, date of admission, health-care cost, principal discharge diagnosis, and the corresponding International Classification of Diseases tenth revision (ICD-10) code following standard procedures. Using this information, we included patients with a primary discharge diagnosis of acute exacerbation of COPD (ICD-10 J44.0-J44.9), who were aged 18 years or older, and who were living in Beijing on a permanent basis. All admissions for acute exacerbation of COPD were from 119 hospitals (68 tertiary and 51 secondary).

**Statistical analysis**

Daily hospitalisations for acute exacerbation of COPD, pollutant concentrations, and meteorological variables in 2013–17 were linked by date to allow a time-series analysis. We defined same-day exposure as lag0 and examined a priori daily exposure up to 4 days (single-day lag0 to lag4 and moving average of lag0–2 and lag0–4 concentrations) before hospitalisation, based on a systematic review. The associations between daily hospitalisations for acute exacerbation of COPD and average concentration of each pollutant were analysed with a generalised additive model estimating Poisson distribution, as follows:

$$\log[E(Y_t)] = \text{intercept} + \beta C_i + ps(\text{calendar time}, 9) + \text{ps(temperature)} + \text{ps(relative humidity)} + \text{public holiday} + \text{day of week}$$

where $E(Y_t)$ represents the number of cases of acute exacerbation of COPD on day $t$; $C$ is the city-averaged concentration; $i$ is the day lag; $\beta$ represents the log-relative risk (RR) of hospitalisation for acute exacerbation of COPD associated with a unit increase in each pollutant mean concentration; ps() indicates penalised spline function to filter out long-term trends and seasonal patterns in daily hospitalisations for acute exacerbation of COPD; temp is the daily mean temperature ($^\circ$C); and RH is relative humidity (%). Public holiday and day of week were included as categorical variables. Degrees of freedom for calendar time, temperature, and relative humidity were selected based on the parameters used in previous studies.

Apart from the single-pollutant models, we also investigated each association in two-pollutant models if Spearman correlation ratios between these pollutants were less than 0·7. Subgroup analyses at lag0 were done by age (18–64 years and ≥65 years), sex, and season (warm season [May to October] or cold season [November to April]). The Z test was used to compare the two estimates derived from each subgroup.

The smoothing function of the generalised additive model was used to graphically analyse the exposure–response relationships between the log-RR of hospitalisation for acute exacerbation of COPD and air pollutant concentrations at lag0.

For each single year from 2013 to 2017, we re-ran the main analyses for the associations between each air pollutant and acute exacerbations of COPD hospitalisation risk at lag0.

We did several sensitivity analyses by altering the generalised additive model: to exclude calendar time, as long-term trends and seasonal patterns might also be partly related to pollutant concentration; to replace calendar time with an interaction term of exposure-by-season; to increase the degrees of freedom of temperature and humidity to six; and to model moving averages for lag0–4 of temperature and humidity instead of the current day (lag0). The latter two analyses were to adjust potential non-linear and lagged confounding effects of weather conditions. Finally, we excluded the 102 days with reconstructed data for PM$_{10}$ from the 1804-day dataset and re-ran the main analysis.

Using the following equation, we calculated the number of cases of acute exacerbations of COPD advanced by PM$_{1·0}$, as an overall air-quality indicator, over the expected rates if daily concentrations had not exceeded the target in each year from 2013 to 2017:
Articles

For O₃ concentrations, which are 8-h averages. PM=particulate matter. NO₂=nitrogen dioxide. SO₂=sulphur dioxide.

Exacerbation of chronic obstructive pulmonary disease in Beijing

Table 1:

Data are for 1804 days (or 1770 days for O₃) from 2013 to 2017. Air pollutant concentrations are 24-h averages, except for PM₂·₅ and PMcoarse, which are 8-h averages. PM=particulate matter. NO₂=nitrogen dioxide. SO₂=sulphur dioxide.

<table>
<thead>
<tr>
<th>Air pollutant concentrations</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM₁₀, μg/m³</td>
<td>10·0</td>
<td>820·0</td>
<td>109·7 (79·1)</td>
<td>91·0 (54·0–140·0)</td>
</tr>
<tr>
<td>PM₂·₅, μg/m³</td>
<td>5·0</td>
<td>467·0</td>
<td>76·7 (66·7)</td>
<td>58·0 (29·0–101·0)</td>
</tr>
<tr>
<td>PMcoarse, μg/m³</td>
<td>0·0</td>
<td>461·0</td>
<td>33·0 (29·1)</td>
<td>27·0 (16·0–41·0)</td>
</tr>
<tr>
<td>NO₂, μg/m³</td>
<td>8·0</td>
<td>155·0</td>
<td>50·5 (24·2)</td>
<td>44·0 (33·0–63·0)</td>
</tr>
<tr>
<td>SO₂, μg/m³</td>
<td>2·0</td>
<td>139·0</td>
<td>15·1 (18·4)</td>
<td>8·0 (4·0–19·0)</td>
</tr>
<tr>
<td>O₃, μg/m³</td>
<td>2·0</td>
<td>292·0</td>
<td>95·8 (62·2)</td>
<td>83·0 (50·0–135·0)</td>
</tr>
<tr>
<td>CO, mg/m³</td>
<td>0·2</td>
<td>8·0</td>
<td>1·2 (1·0)</td>
<td>0·9 (0·6–1·4)</td>
</tr>
</tbody>
</table>

Meteorological measures

<table>
<thead>
<tr>
<th></th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature, °C</td>
<td>-16·0</td>
<td>32·0</td>
<td>13·1 (11·0)</td>
<td>14·0 (2·0–23·0)</td>
</tr>
<tr>
<td>Relative humidity, %</td>
<td>8·0</td>
<td>97·0</td>
<td>53·2 (20·1)</td>
<td>53·0 (38·0–69·5)</td>
</tr>
</tbody>
</table>

Hospital admissions (number of cases per day)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Female</th>
<th>Male</th>
<th>Age &lt;65 years</th>
<th>Age ≥65 years</th>
<th>Cool season, May to October</th>
<th>Warm season, November to April</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17</td>
<td>2</td>
<td>9</td>
<td>0</td>
<td>13</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Total admissions</td>
<td>220</td>
<td>90</td>
<td>153</td>
<td>43</td>
<td>184</td>
<td>168</td>
<td>220</td>
</tr>
<tr>
<td>Female admissions</td>
<td>89</td>
<td>29</td>
<td>60</td>
<td>14</td>
<td>75</td>
<td>80</td>
<td>99</td>
</tr>
<tr>
<td>Male admissions</td>
<td>13</td>
<td>13</td>
<td>93</td>
<td>14</td>
<td>75</td>
<td>80</td>
<td>122</td>
</tr>
<tr>
<td>Age &lt;65 years admissions</td>
<td>14</td>
<td>14</td>
<td>60</td>
<td>14</td>
<td>75</td>
<td>80</td>
<td>122</td>
</tr>
<tr>
<td>Age ≥65 years admissions</td>
<td>75</td>
<td>75</td>
<td>93</td>
<td>75</td>
<td>75</td>
<td>80</td>
<td>122</td>
</tr>
</tbody>
</table>

Table 1: Air pollutant concentrations, weather conditions, and daily hospital admissions for acute exacerbation of chronic obstructive pulmonary disease in Beijing

Where PMₜ was the city-wide average concentration of PM₂·₅ on day t; PARF represents the population-attributable risk fraction, calculated as (RR–1) divided by RR, assuming the prevalence of air pollution exposure was 100%; and N is the daily mean number of cases in a particular year.

All statistical analyses were done in R (version 3.0.2) using the MGCV, DPLYR, and TTR packages. RR of hospitalisation for acute exacerbation of COPD per IQR increase for each air pollutant were calculated.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

During 2013–17, the daily mean concentration of PM₁₀ was 109·7 μg/m³ and of PM₂·₅ was 76·7 μg/m³ (table 1), both of which were considerably higher than the current Chinese grade I ambient air-quality standard (target 24-h mean concentrations 50 μg/m³ for PM₁₀ and 35 μg/m³ for PM₂·₅) or WHO guidelines (target 50 μg/m³ for PM₁₀ and 25 μg/m³ for PM₂·₅). 161

Over the 5-year period studied, annual mean SO₂ concentration decreased by 68% (from 24·5 μg/m³ [SD 23·2] in 2013 to 7·7 μg/m³ [8·4] in 2017) and PM₂·₅ concentration by 33% (from 86·8 μg/m³ [65·8] to 57·7 μg/m³ [55·5]), whereas the concentration of O₃ remained stable (figure 1; appendix p 5). Concentrations of PM₁₀, PM₂·₅, NO₂, and CO were lowest in summer (June to August) and highest in winter (November to February) (appendix p 6), but the opposite trend was observed for O₃. Concentrations of PMcoarse were consistently higher in spring (March to May), PM₁₀, PM₂·₅, NO₂, and CO concentrations showed strong positive correlations with each other (Spearman’s ρ>0·7), whereas PM₁₀ and PM₂·₅ showed a weak positive correlation (ρ=0·247; appendix p 9). SO₂ concentration showed moderate positive correlations with concentrations of PM₁₀, PM₂·₅, and NO₂, and CO (ρ=0·4 to <0·7).

In single-pollutant models at lag 0, the RR of hospitalisation for acute exacerbation of COPD per IQR increase in pollutant was 1·029 (95% CI 1·023–1·035) for PM₁₀, 1·028 (1·021–1·034) for PM₂·₅, and 1·019 (1·013–1·024) for SO₂, whereas PMcoarse and PM₂·₅ showed a weak positive correlation (ρ=0·247; appendix p 9). SO₂ concentration showed moderate positive correlations with concentrations of PM₁₀, PM₂·₅, and NO₂, and CO (ρ=0·4 to <0·7)

In the warm season, increased O₃ exposures at lag0 and lag0–2 were significantly associated with increased...
Figure 2: RR of hospitalisation for acute exacerbation of COPD associated with pollutants in single-pollutant and two-pollutant models at different lag days during 2013–17

Data are RR (95% CI) per IQR increment of pollutant concentration. CO=carbon monoxide. NO₂=nitrogen dioxide. O₃=ozone. PM=particulate matter. RR=relative risk. SO₂=sulphur dioxide.
Table 2: Associations between daily average concentration of O₃ (per IQR of 85 μg/m³ higher) and daily hospital admissions for acute exacerbation of chronic obstructive pulmonary disease in Beijing (2013–17, 1770 days) in single-pollutant and two-pollutant models

<table>
<thead>
<tr>
<th>Lag</th>
<th>O₃ only</th>
<th>O₃ and PM₁₀</th>
<th>O₃ and PM_coarse</th>
<th>O₃ and PM₂·₅</th>
<th>O₃ and NO₂</th>
<th>O₃ and CO</th>
<th>O₃ and SO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm season (May to October)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lag0</td>
<td>1·027 (1·016–1·044)*</td>
<td>1·008 (0·991–1·025)</td>
<td>1·022 (1·005–1·039)*</td>
<td>1·006 (0·989–1·023)</td>
<td>1·025 (1·008–1·042)*</td>
<td>1·025 (1·008–1·042)*</td>
<td>1·018 (1·001–1·035)*</td>
</tr>
<tr>
<td>Lag1</td>
<td>1·019 (1·004–1·035)*</td>
<td>1·009 (0·994–1·025)</td>
<td>1·017 (1·001–1·033)*</td>
<td>1·011 (0·996–1·027)</td>
<td>1·019 (1·004–1·035)*</td>
<td>1·019 (1·004–1·034)*</td>
<td>1·015 (0·999–1·031)</td>
</tr>
<tr>
<td>Lag2</td>
<td>1·004 (0·990–1·018)</td>
<td>0·996 (0·982–1·011)</td>
<td>1·002 (0·988–1·016)</td>
<td>0·997 (0·983–1·012)</td>
<td>1·004 (0·989–1·018)</td>
<td>1·003 (0·989–1·018)</td>
<td>1·003 (0·988–1·019)</td>
</tr>
<tr>
<td>Lag3</td>
<td>1·000 (0·986–1·014)</td>
<td>0·994 (0·979–1·008)</td>
<td>0·998 (0·984–1·013)</td>
<td>0·994 (0·980–1·009)</td>
<td>0·999 (0·985–1·013)</td>
<td>1·000 (0·986–1·014)</td>
<td>1·002 (0·987–1·017)</td>
</tr>
<tr>
<td>Lag4</td>
<td>0·995 (0·982–1·009)</td>
<td>0·991 (0·977–1·006)</td>
<td>0·993 (0·980–1·007)</td>
<td>0·993 (0·978–1·007)</td>
<td>0·994 (0·980–1·008)</td>
<td>0·995 (0·981–1·009)</td>
<td>0·991 (0·976–1·005)</td>
</tr>
<tr>
<td>Lag0–2</td>
<td>1·027 (1·007–1·048)*</td>
<td>1·006 (0·985–1·027)</td>
<td>1·019 (0·998–1·040)</td>
<td>1·010 (0·989–1·030)</td>
<td>1·028 (1·008–1·048)*</td>
<td>1·026 (1·006–1·047)*</td>
<td>1·016 (0·995–1·038)</td>
</tr>
<tr>
<td>Lag0–4</td>
<td>1·019 (0·996–1·042)</td>
<td>1·001 (0·978–1·025)</td>
<td>1·011 (0·988–1·034)</td>
<td>1·006 (0·983–1·029)</td>
<td>1·023 (1·000–1·047)</td>
<td>1·019 (0·997–1·043)</td>
<td>1·007 (0·983–1·032)</td>
</tr>
<tr>
<td>Cool season (November to April)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lag0</td>
<td>0·952 (0·916–0·969)*</td>
<td>0·957 (0·941–0·974)*</td>
<td>0·960 (0·943–0·977)*</td>
<td>0·955 (0·938–0·971)*</td>
<td>0·964 (0·947–0·982)*</td>
<td>0·966 (0·949–0·984)*</td>
<td>0·955 (0·938–0·972)*</td>
</tr>
<tr>
<td>Lag1</td>
<td>0·970 (0·956–0·985)*</td>
<td>0·982 (0·967–0·998)*</td>
<td>0·975 (0·960–0·989)*</td>
<td>0·979 (0·963–0·995)*</td>
<td>0·984 (0·967–1·002)</td>
<td>0·989 (0·973–1·007)</td>
<td>0·975 (0·960–0·991)*</td>
</tr>
<tr>
<td>Lag2</td>
<td>0·991 (0·977–1·005)</td>
<td>0·997 (0·982–1·012)</td>
<td>0·992 (0·987–1·006)</td>
<td>0·996 (0·981–1·011)</td>
<td>0·993 (0·977–1·009)</td>
<td>1·001 (0·985–1·018)</td>
<td>0·989 (0·975–1·004)</td>
</tr>
<tr>
<td>Lag3</td>
<td>0·988 (0·974–1·001)</td>
<td>0·989 (0·975–1·004)</td>
<td>0·988 (0·972–1·002)</td>
<td>0·988 (0·974–1·003)</td>
<td>0·980 (0·965–0·996)*</td>
<td>0·989 (0·973–1·005)</td>
<td>0·986 (0·972–1·001)</td>
</tr>
<tr>
<td>Lag4</td>
<td>0·988 (0·975–1·002)</td>
<td>0·990 (0·976–1·005)</td>
<td>0·989 (0·975–1·003)</td>
<td>0·988 (0·973–1·003)</td>
<td>0·979 (0·963–0·995)*</td>
<td>0·988 (0·972–1·005)</td>
<td>0·986 (0·972–1·001)</td>
</tr>
<tr>
<td>Lag0–2</td>
<td>0·956 (0·937–0·976)*</td>
<td>0·969 (0·948–0·980)*</td>
<td>0·963 (0·943–0·983)*</td>
<td>0·964 (0·943–0·985)*</td>
<td>0·970 (0·948–0·992)*</td>
<td>0·973 (0·957–1·002)</td>
<td>0·959 (0·939–0·979)*</td>
</tr>
<tr>
<td>Lag0–4</td>
<td>0·960 (0·939–0·981)*</td>
<td>0·972 (0·950–0·994)*</td>
<td>0·963 (0·942–0·984)*</td>
<td>0·967 (0·945–0·989)*</td>
<td>0·961 (0·940–0·987)*</td>
<td>0·980 (0·955–1·005)</td>
<td>0·961 (0·940–0·987)*</td>
</tr>
</tbody>
</table>

Data are relative risk (95% CI). O₃=ozone. PM=particulate matter. NO₂=nitrogen dioxide. CO=carbon monoxide. SO₂=sulphur dioxide. *Statistically significant (p<0·05).

The number of days that city-averaged PM₁₀ concentration exceeded the WHO 24-h target (25 μg/m³) was reduced from 298 in 2013 to 256 in 2017 (table 3). There was a decreasing trend in the number of cases of acute exacerbations of COPD advanced by PM₁₀ pollution above the expected rates if daily concentrations had not exceeded either the Chinese or WHO targets (table 3). Based on the WHO 24-h target, the number of acute exacerbations of COPD cases advanced by PM₁₀ was 12679 in 2013 and 7377 in 2017, corresponding to a decrease of nearly 42% between those two timepoints. A similar percentage reduction was observed for healthcare cost (table 3).

**Discussion**

We found significant associations between short-term exposures to air pollution and hospitalisations for acute exacerbation of COPD, with RR in lag0 ranging from 1·018 to 1·036 for each IQR increase in concentration. By lag4, most of these increased risks became non-significant. Effects of moving-day average exposures (lag0–2 and lag0–4) were also statistically significant and similar to those seen at lag0. Women and patients aged 65 years or older were most susceptible. The shapes of each exposure–response relationship varied greatly by type of pollutant in our study, which probably reflects the variations in biological mechanisms and characteristics, including toxicity, of each pollutant.

Our effect estimates expressed per 10 μg/m³ increase of PM₂·₅, concentration exceeded the WHO 24-h target (25 μg/m³) was reduced from 298 in 2013 to 256 in 2017 (table 3). There was a decreasing trend in the number of cases of acute exacerbations of COPD advanced by PM₂·₅ pollution above the expected rates if daily concentrations had not exceeded either the Chinese or WHO targets (table 3). Based on the WHO 24-h target, the number of acute exacerbations of COPD cases advanced by PM₂·₅ was 12679 in 2013 and 7377 in 2017, corresponding to a decrease of nearly 42% between those two timepoints. A similar percentage reduction was observed for healthcare cost (table 3).
(1·004 [95% CI 1·003–1·005]; appendix p 25) was lower than those reported in previous studies of Beijing residents conducted in 2010–12 (1·007 [1·006–1·007]) and in 2013 (1·015 [1·001–1·028]).

APPCAP has mainly targeted heavy industries and has resulted in an appreciable reduction in concentrations of SO2 and PM10 in Beijing. It is likely that the compositions of air pollutant mixtures will have changed (eg, lower sulphur compositions) over the years, and that these changes could have positive effects on health. A 2018 study of 74 cities in China estimated substantial reductions in mortality as an effect of APPCAP. This finding is further supported by our estimation of decreased numbers of cases of acute exacerbations of COPD advanced by PM2·5 pollution, highlighting the effectiveness of such air pollution control policy in reducing respiratory morbidity. However, lasting health benefits from improved air quality remain to be confirmed. A long-term, multidimensional air pollution control strategy is needed in China to safeguard public health and reduce health-care costs.

It has been hypothesised that air pollutants could induce airway epithelial damage, inhibit mucociliary clearance, and impair macrophage function through activation of inflammatory cells and their mediators as well as through promotion of intracellular oxidative stress. These pathways might either directly trigger an exacerbation, or collectively create a pulmonary microenvironment with impaired immune function that makes the host more susceptible to viral and bacterial infections—the major causes of acute exacerbations of COPD. Besides the physical and chemical compositions of pollutants that might, in part, underlie the mechanisms leading to acute exacerbations of COPD, some airborne microbes (eg, pathogenic bacteria and fungi) might also play a role.

Relatively few studies have investigated the short-term effects of PMcoarse on acute exacerbations of COPD. In our study, the exposure–response curve followed a non-linear pattern, being steeper at lower concentrations but shallower at higher concentrations, and no saturation effect was evident. This finding indicates that PMcoarse (or, similarly, PM10), even at a relatively low concentration, could increase risk of acute exacerbation events in COPD, although the threshold for so-called safe concentrations remains to be established. Previous studies have reported that PMcoarse has short-term health effects at least as strong as those of PM10, but the effects of PMcoarse were generally higher for respiratory than for cardiovascular outcomes because of the physical and chemical differences in these particles. Unlike PM10, which can

Figure 3: Exposure–response relationships between each pollutant and hospitalisation for acute exacerbation of COPD in single-pollutant models at lag0 during 2013–17.

Red tick marks along the x-axes represent individual observations. CO=carbon monoxide. COPD=chronic obstructive pulmonary disease. NO2=nitrogen dioxide. O3=ozone. PM=particulate matter. RR=relative risk. SO2=sulphur dioxide.
travel deep into the respiratory system to the alveoli and terminal bronchioles, and even cross the air–blood barrier. PM_{coarse} is mainly deposited in the primary bronchi. PM_{coarse} is formed of more visible forms of PM, including road dust, soil, and black smoke. In epidemiological studies, PM_{coarse}, but not PM_{2·5}, was associated with an increased prevalence of respiratory symptoms, indicating that PM_{coarse} might have a greater role in the triggering of acute exacerbations of COPD than does PM_{2·5}. Beijing is often affected by dust storms with extremely high concentrations of coarse particles, and studies have suggested a link between these dust storms and hospitalisations for respiratory disease. The significance of our findings for PM_{coarse} appeared unaffected by adjustment for PM_{2·5}, but epidemiological and toxicological evidence of the effects of coarse particles on respiratory outcomes warrants further investigation.

Very few studies from Asia have explored the acute effects of CO and the risk of acute exacerbations of COPD. In our study, we observed a 3% increase in acute exacerbations of COPD per 1 mg/m³ increase in CO at lag0 (appendix p 13), consistent with pooled estimates reported for Europe (4%) and North America (2%). However, two studies in Shanghai and Hong Kong have shown that low ambient concentrations of CO are protective against COPD exacerbation, even after co-adjusting for other traffic-related pollutants. Both studies cautiously suggested that this link is possible because low concentrations of CO can have anti-inflammatory and antimicrobial effects, as reported in both experimental and human studies. Our study had similarly low concentrations of CO, but the correlations between CO and other traffic-related pollutants (PM_{10} and NO_{x}) in our study were high, which precluded co-adjustments with these pollutants.

Ambient concentrations of SO_{2} in China have decreased markedly since 2013, as supported by our data, mainly because of strict control measures among industries and a steady structural change in energy consumption. Despite this reduction, over this 5-year period, we found a modest positive association between SO_{2} and hospitalisations for acute exacerbations of COPD, even after adjusting for PM_{2·5}. The significant association between exacerbations and SO_{2} observed in 2013 seem to diminish over the years to 2017, a pattern that was not seen for other pollutants. However, this finding needs cautious interpretation until air pollution concentrations for future years become available to allow the effects of long-term air-quality improvement on health gains to be studied.

The concentrations of O_{3} remained stable from 2013–17. Background O_{3} concentrations might remain relatively constant for many years in urban areas in China, and even increase if measures against nitrogen oxides (NO_{x}) emissions are adopted rigorously, as shown in Europe and North America. The Global Burden of Disease study estimated that about 254,000 deaths from COPD in 2015 were attributable to O_{3}. Given this context, and that our results for O_{3} during the warm season were robust to adjustments for some other gaseous pollutants, continuous monitoring and mitigation measures for O_{3} are needed.

The seasonal effects of O_{3} on acute exacerbations of COPD remain unclear, as we observed positive associations in the warm season but negative associations in the cold season. In Beijing, concentrations of O_{3} during the warm season are high, and people tend to go outdoors and open windows more often; in the cold season, concentrations are low, while people mostly stay indoors and ventilation is reduced because of heating. These differential behaviours of individuals could also partly explain the higher effect estimates for PM_{10} and PM_{2·5} in the warm season. Additionally, high temperatures might have a synergistic role. As with two other studies of Beijing residents, we found that women with COPD were more susceptible to acute air pollution effects. Patients aged 65 years and older were also susceptible because they are likely to have a compromised immune system, and the health of patients with COPD generally deteriorates rapidly after 65 years of age.

As with many previous studies, we have only considered the temporal variations of the effects of air pollutants on hospitalisations for acute exacerbations of COPD. However, spatial variations of these health effects should not be disregarded, especially in megacities such as Beijing, where spatial variation in concentrations of air pollutants could vary greatly. The southern part of Greater Beijing reportedly has worse air quality than that in the northern part, while monitoring stations near...
traffic or in the city centre have (as expected) the highest concentrations of some pollutants. In addition, confounding factors operate at the area level across the city, which might also affect the spatial variations of the health effects. For example, a study in Beijing reported that, despite the lower air pollution concentration in suburban and rural areas compared with urban areas, cardiovascular mortality risk in relation to air pollution was higher in suburban and rural areas than in urban areas. Although different compositions of air pollutants across the areas probably contribute to this effect, factors such as access to quality health care, age structure of populations, and availability of protection measures also contribute. Beyond the scope of this study, a separate, careful investigation involving the collection of station-specific air quality data and contextual area-level data would be needed to understand the spatial variations of acute exacerbations of COPD risks in Beijing.

This is by far the largest time-series study in China to study the short-term effects of air pollution on hospitalisations for acute exacerbations of COPD among the whole population of Beijing at a time when various measures were being implemented to reduce air pollution. Our study had some limitations. First, because this was an ecological analysis in which individual-level confounding factors were not considered, modelled estimates should not be interpreted as predictive of individual hospitalisation probability. Some factors are unlikely to change over a short period, but time-varying factors such as seasonal viral or bacterial infection patterns might confound the studied relationships. Second, we only had data on daily, outdoor, city-wide average concentrations of each air pollutant, which we correlated with daily hospitalisations for acute exacerbation of COPD in the whole of Beijing. This method will have introduced bias to health estimates because place of residence and time-activity (eg, time spent indoors, including in the home and workplace, and the associated exposures to indoor sources) were not taken into account. People spend most of their time indoors, and outdoor pollution does penetrate indoors but with variable infiltration efficiency. This exposure misclassification is likely to underestimate, although not necessarily invalidate, the effect estimate. Furthermore, assigning estimates from the nearest monitoring station to residence did not necessarily improve the correlation between personal exposures and ambient concentrations. Ongoing studies using personal air pollution monitoring will be useful to bridge this gap. Third, our study outcome was confined to acute exacerbation of COPD, which might only represent the most severe cases. Air pollution can also have specific effects on different types of exacerbations, and these effects should be investigated further if data became available. Fourth, as the air pollution concentration in Beijing was in decline over the study years, there might have been fewer deaths among patients with COPD and thus the existing COPD populations might have increased in size, which could have affected our estimates. Finally, other than effective emission control measures, trends in economic development, meteorological conditions, and health care might all contribute to air quality and health management, and these contributions should be carefully considered in future investigations. In conclusion, acute exposures to both particulate and gaseous pollutants were significantly associated with hospitalisations for acute exacerbation of COPD in Beijing. Although the APPCAP has shown positive effects in terms of reducing air pollution and COPD morbidity in our study population, the concentrations of ambient air pollution are still dangerously high, warranting continued collective mitigation measures to achieve substantial health benefits.

Contributors LL, YC, and ZT conceived and designed the study. YC and LL wrote the report. LL, DZ, and BL contributed to data collection. LL and YC did the statistical analysis. YC, LL, DZ, BB, BL, WX, QC, ALH, FJK, and ZT contributed to the discussion and interpretation of findings, revised the manuscript, and approved the final submission.

Declaration of interests We declare no competing interests.

Acknowledgments We thank the data collection teams. This study received funding from the Medical Research Council—Public Health England (MRC-PHE) Centre for Environment and Health (grant number MR/L01341X/1). YC is supported by a MRC Early-Career Research Fellowship awarded through the MRC-PHE Centre for Environment and Health (grant number MR/M501669/1).

References
inhalable microbial communities in PM2.5 in Beijing city, China.

Du P, Du R, Ren W, Lu Z, Fu P. 

Kelly FJ, Fussell JC. Air pollution and airway disease. 

Malawi M, Mukaka MM. Statistics corner: a guide to appropriate use of penalized splines. 


Tian Y, Xiang X, Juan J, et al. Short-term effects of ambient fine particulate matter pollution on hospital visits for chronic obstructive pulmonary disease in Beijing, China. 


Goeran K, Tatyana K, Willi S. Filtering time series with penalized splines. 

Wang YQ, Zhang XY, Sun JY, Zhang XC, Che HZ, Li Y. Spatial and temporal variations of the concentrations of PM2.5, PM10, and PM, in China. 

Xie W, Li G, Zhao D, et al. Relationship between fine particulate air pollution and ischaemic heart disease morbidity and mortality. 

Wu D, Lam TP. Underuse of primary care in China: the scale, causes, and solutions. 

Goeran K, Tatyana K, Willi S. Filtering time series with penalized splines. 


Tian Y, Xiang X, Juan J, et al. Short-term effects of ambient fine particulate matter pollution on hospital visits for chronic obstructive pulmonary disease in Beijing, China. 


Mukaka MM. Statistics corner: a guide to appropriate use of correlation coefficient in medical research. 


Kelly FJ, Fussell JC. Air pollution and airway disease. 


Adar SD, Filgrana PA, Clements N, Peel JL. Ambient coarse particle pollution and respiratory symptoms in individuals having either asthma or chronic obstructive pulmonary disease: a systematic review and meta-analysis. 

Kelly FJ, Fussell JC. Size, source and chemical composition as determinants of toxicity attributable to ambient particulate matter. 

Cai J, Chen R, Wang W, Xu X, Hu S, Kan H. Does ambient CO have protective effect for COPD patients? 


Wang YQ, Zhang XY, Sun JY, Zhang XC, Che HZ, Li Y. Spatial and temporal variations of the concentrations of PM2.5, PM10, and PM, in China. 


Vingarzan R. A review of surface ozone background levels and trends. 


Chen W, Tang H, Zhao H. Diurnal, weekly and monthly spatial variations of air pollutants and air quality of Beijing. 


Elbott ST, Petkau AJ, Vedal S, Fisher TV, Brauer M. Exposure of chronic obstructive pulmonary disease patients to particulate matter: relationships between personal and ambient air concentrations. 

Moore E, Chatzidiakou L, Jones RL, et al. Linking e-health records, patient-reported symptoms and environmental exposure data to characterise and model COPD exacerbations: protocol for the COPE study. 

Pfeffer PE, Donaldson GC, Mackay AJ, Wedzicha JA. Increased chronic obstructive pulmonary disease exacerbations of likely viral etiology follow elevated ambient nitrogen oxides. 

Greenbaum D. Making measurable progress in improving China’s air and health. 

Cai J, Chen R, Wang W, Xu X, Hu S, Kan H. Does ambient CO have protective effect for COPD patients? 


Wang YQ, Zhang XY, Sun JY, Zhang XC, Che HZ, Li Y. Spatial and temporal variations of the concentrations of PM2.5, PM10, and PM, in China. 

Xie W, Li G, Zhao D, et al. Relationship between fine particulate air pollution and ischaemic heart disease morbidity and mortality. 

Wu D, Lam TP. Underuse of primary care in China: the scale, causes, and solutions. 

Goeran K, Tatyana K, Willi S. Filtering time series with penalized splines. 


Tian Y, Xiang X, Juan J, et al. Short-term effects of ambient fine particulate matter pollution on hospital visits for chronic obstructive pulmonary disease in Beijing, China. 


Mukaka MM. Statistics corner: a guide to appropriate use of correlation coefficient in medical research. 


Kelly FJ, Fussell JC. Air pollution and airway disease. 


Adar SD, Filgrana PA, Clements N, Peel JL. Ambient coarse particle pollution and respiratory symptoms in individuals having either asthma or chronic obstructive pulmonary disease: a systematic review and meta-analysis. 


Kelly FJ, Fussell JC. Size, source and chemical composition as determinants of toxicity attributable to ambient particulate matter. 


Environ Health 2012; 11: 75. 


Pfeffer PE, Donaldson GC, Mackay AJ, Wedzicha JA. Increased chronic obstructive pulmonary disease exacerbations of likely viral etiology follow elevated ambient nitrogen oxides. 


Greenbaum D. Making measurable progress in improving China’s air and health. 

Lancet Planet Health 2018; 2: e289–90.