Association of air pollution with the risk of initial outpatient visits for tuberculosis in Wuhan, China

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ABSTRACT

Objectives Previous studies suggested the association of air pollution with initial Mycobacterium tuberculosis infection and the disease development. However, few studies have been conducted on air pollution and initial tuberculosis (TB) consults using short-interval data. We investigated the weekly association between air pollution and initial TB outpatient visits.

Methods We used a Poisson regression model combined with a distributed lag non-linear model to conduct a time-series study with weekly air pollution data and TB cases during 2014–2017 in Wuhan, China.

Results A 10 µg/m³ increase in NO₂ (nitrogen dioxide) was associated with −11.74% (95% CI: 0.70 to 23.98, lag 0–1 weeks), 21.45% (95% CI: 1.44 to 45.41, lag 0–2 weeks) and 12.7% (95% CI: 0.97 to 26.02, lag 0–1 weeks) increase in initial TB consults among all patients with TB, old patients (≥60 years old) and male ones, respectively. A 10 µg/m³ increase in SO₂ (sulfur dioxide) was associated with −22.23% (95% CI: −39.23 to −0.49, lag 0–16 weeks), −28.66% (95% CI: −44.3 to −8.58, lag 0–16 weeks), −23.85% (95% CI: −41.79 to −4.39, lag 0–16 weeks) increase in initial TB consults among all patients with TB, old patients (≥60 years old) and male ones, respectively. A 0.1 mg/m³ increase in CO (carbon monoxide) and a 10 µg/m³ increase in PM₁₀ (particulate matter) were separately associated with 42.32% (95% CI: 1.16 to 100.22, lag 0–2 weeks) and 17.38% (95% CI: 0.28 to 37.38, lag 0–16 weeks) increases in TB consults.

Conclusion Our study first highlighted the importance of weekly association between air pollution and the risk of initial TB consults, which is helpful for the arrangements of TB screening and medical assistance.

INTRODUCTION

Tuberculosis (TB) has become the world’s ninth leading cause of death and continues to pose great threats to human health.1 China is among the global top 22 high-TB burden countries and has the third largest number of patients with TB in the world.1 TB is caused by the bacterium Mycobacterium tuberculosis. Individuals with suppressed host immune system conditions, such as HIV pandemic, diabetes and end-stage renal failure, were particularly susceptible to TB.2 In recent years, worldwide attention has increasingly extended to the association of ambient air pollution with TB cases. A majority of individual-based and population-based studies reported the association of TB cases with long-term air pollution exposure. In view of individual 2-year average exposure of air pollution, a nested case–control study in Northern California and a cohort study of Taiwan residents both revealed a positive correlation of nitrogen dioxide (NO₂) with TB incidence.3 4 Ecological studies also showed the associations between annual average exposure of ambient air pollution with TB.5 6 A study in North Carolina suggested that exposure of particulate matter (PM) potentially increased the susceptibility to TB development.7 8 A study conducted by Hwang et al9 in South Korea found a positive association of sulfur dioxide (SO₂) with TB incidence. However, there are less investigation on the association of air pollution with reported TB cases using empirical and short-interval data. Only in most recent years, a couple of studies were
undertaken to examine the association. Analysing monthly data, You et al. observed a stable link between incremental aerodynamic diameter of $\leq 2.5 \mu m$ (PM$_{2.5}$) concentration and increase in TB cases. Using daily data, Zhu et al. found that increased level of NO$_2$ and SO$_2$ positively and independently correlated with newly reported TB cases, while Ge et al.'s group reported an inverse association of SO$_2$ exposure with initial TB outpatient visits.

The current epidemiological studies have suggested associations between air pollution and initial *M. tuberculosis* infection and disease development. However, relevant research on the impact of incremental level of air pollution on initial TB outpatient visits using short-interval data is still lacking. Given that patients with TB are often accompanied by chronic symptoms for several weeks before their initial outpatient visits and using relevant data at the level of a month could not distinguish lag-specific effects from week to week, we aimed to explore whether weekly (7 days) exposure to PM$_{10}$, PM$_{2.5}$, SO$_2$, NO$_2$ and carbon monoxide (CO) was associated with the risk of weekly TB cases for initial outpatient visits in Wuhan, to elucidate the risk of TB consults caused by fluctuations of air pollution concentrations.

**MATERIALS AND METHODS**

**Study area**

Wuhan (centre: 114.3°E, 30.6°N), the capital of Hubei Province, is the largest city in Central China and has moist subtropical monsoon climate. It is located on the eastern part of the Jianghan Plain, middle and lower reaches of the Yangtze River and covers a total area of 8494.41 km$^2$ with a permanent population of 10.914 million at the end of 2017.

**Data on outpatients with TB**

Daily cases of newly diagnosed TB in Wuhan from year 2014 to 2017 were obtained from online national infectious disease reporting system, which was offered by Hubei Provincial Center for Disease Control and Prevention. We also collected demographic information of each TB case, including age, sex and dates of initial TB outpatient visits. In clinical practice, it is difficult to distinguish whether newly diagnosed TB cases were caused by initial infection or reactivated via endogenous factors after some weeks or years. Thus, the active TB cases in this study included newly infected cases and reactivated TB cases.

**Air pollution and climate data**

Daily average values of air pollution were obtained from China’s National Urban Air Quality Real-time Publishing Platform (http://106.37.208.233:20053), including PM$_{10}$, PM$_{2.5}$, SO$_2$, NO$_2$, and CO. Meteorological parameters, including daily mean temperature, relative humidity, air pressure, rainfall, wind speed and duration of sunshine, were derived from China Meteorological Data Sharing Service System (http://cdc.cma.gov.cn). The locations of air quality monitoring stations and meteorological monitoring stations in Wuhan were shown on a map (online supplementary eFigure 1). The weekly (7 days) average values of air pollution concentrations, meteorological measurements and weekly total number of TB cases of the whole city were calculated to examine the effects of air pollution on initial TB consults.

**Distributed lag non-linear model (DLNM)**

As DLNM can reveal the additional lag dimension of the exposure–response relationship, we fitted a DLNM to assess non-linear exposure–response relationship and lag effects of air pollution on the risk of initial TB consults. Suppose that $Y_t$ denotes the number of TB cases of the whole city at calendar time (week) $t$ and follows a Poisson distribution by $Y_t \mid \mu_t \sim \text{Poi}(\mu_t)$, where $\mu_t$ is the expected value of $Y_t$. Hence, a log-linear Poisson model which allows for overdispersion to combine a DLNM was applied. The single-pollutant model specifications used for estimating the relationship between pollution and initial TB cases at each single-week lag were as follows:

$$
\begin{align*}
\log(\mu_t) &= \alpha + \beta \text{AP}_{t,l} + \text{ns}(\text{temp}, 3) + \text{ns}(\text{humidity}, 3) \\
&\quad + \text{ns}(\text{wind}, 3) + \text{ns}(\text{sunshine}, 3) + \lambda \text{year} \\
&\quad + \text{ns}(\text{time}, 6) + \delta \text{Spring Festival} \\
&= \alpha + \beta \text{AP}_{t,l} + \text{COV}_S
\end{align*}
$$

(1)

where $\alpha$ is the intercept, and $\text{AP}_{t,l}$ is the cross-basis matrix by using a double natural cubic spline DLNM to each indicator of air pollution (AP); $\beta$ is the coefficient for $\text{AP}_{t,l}$ and $l$ is the maximum lag time up to 16 weeks; $\lambda$ and $\delta$ stand for coefficients of the dummy variables for year and the Spring Festival. The time spline function concerning the week is a natural cubic spline to account for seasonality with 6 df, which was determined based on the model fit using Akaike’s information criterion. We fitted natural cubic splines with a priori 3 df to control for meteorological variables as covariates. The detailed descriptions for the choices of basis types, number and placement of knots and maximum lag weeks in this model and the selection for covariates were included in the online supplementary files (Section 2, including online supplementary eTables 1–2).

We used excess risk (ER) estimates, which represented as the percentage change in initial TB outpatient visits per 10-unit increase of air pollutants, to assess lag-specific and cumulative effects of air pollution on initial TB outpatient visits over lagged 16 weeks in the single-pollutant models. Then, stratification analysis by age and sex was performed to separately model the effects of air pollution in subgroups. Children (<15 years old) were excluded from the subgroup analyses as the sample size of this group was only 140 (0.6%), similar to that of 0.5% prevalence of the Ningbo study of China. In addition, as the two peak months of TB incidence in Wuhan are during March to April and August to September compared with the trough month (December) of TB incidence, the analysis was stratified by ‘peak season’ (from March to August) and ‘trough season’ (from September to February in next year) of TB incidence. Besides, we also used daily data to explore the association between air pollution and initial TB outpatient visits in the single-pollutant models in total population and subgroups stratified by age and sex, the detailed methods were described in the online supplementary files (Section 5).

Finally, we conducted several sensitivity analyses to assess the robustness of our main results by: (1) fitting two-pollutant models, (2) excluding 1331 (5.3%) retreated TB, (3) changing the length of maximum lag weeks to 12 and 24 weeks in the DLNM, (4) using 7 df and 4 df in the splines on time and meteorological factors, respectively.

The proportion of missing data in our study was 0.2% and missing values were interpolated using the averages of the data in the previous and the following days. Our data analysis was done using the dlnm packages in R (version 3.5.0). We mapped the positions of air pollutant and weather monitoring stations using ArcGIS (v.10.5).
Environment

Table 1  Summarised statistics of weekly TB cases, air pollution and meteorological variables in Wuhan, 2014–2017 (n=25077)

| Variable                  | Mean±SD | P1  | P25 | P50  | P75  | P99  |
|---------------------------|---------|-----|-----|------|------|------|
| Weekly TB cases           |         |     |     |      |      |      |
| Total                     | 120.0±25.5 | 53  | 105 | 121  | 136  | 179  |
| Male                      | 83.5±19.0 | 30  | 72  | 83   | 95   | 127  |
| Female                    | 36.5±9.5  | 16  | 30  | 36   | 43   | 58   |
| Children, 0–14 years      | 0.7±0.9 | 0   | 0   | 1    | 3    |      |
| Young, 15–59 years        | 83.9±18.4 | 34  | 72  | 83   | 96   | 127  |
| Middle aged and older, ≥60 years | 35.4±9.6 | 12  | 31  | 35   | 41   | 62   |
| Pollutant concentration   |         |     |     |      |      |      |
| PM<sub>2.5</sub> (μg/m<sup>3</sup>) | 64.9±35.7 | 17.0 | 41.0 | 56.0 | 84.0 | 178.6 |
| PM<sub>10</sub> (μg/m<sup>3</sup>) | 101.2±40.6 | 32.6 | 70.0 | 97.0 | 123.0 | 210.1 |
| SO<sub>2</sub> (μg/m<sup>3</sup>) | 18.5±12.7 | 4.0  | 9.0  | 16.0 | 23.0 | 71.9  |
| NO<sub>2</sub> (μg/m<sup>3</sup>) | 49.7±15.4 | 25.2 | 38.0 | 48.0 | 57.0 | 93.9  |
| CO (mg/m<sup>3</sup>)      | 1.1±0.3  | 0.6  | 0.9  | 1.0  | 1.2  | 2.2   |
| Meteorology measure       |         |     |     |      |      |      |
| Mean average temperature (°C) | 17.3±8.5  | 1.9  | 9.4  | 18.6 | 2.5  | 32.2  |
| Relative humidity (%)     |          | 77.1±9.1 | 55.1 | 71.0 | 78.0 | 85.0 | 94.0  |
| Air pressure (hPa)        |          | 1010.2±8.6 | 996.7 | 1002.6 | 1010.6 | 1017.7 | 1025.6 |
| Wind velocity (m/s)       |          | 2.0±0.4 | 1.3  | 1.7  | 2.0  | 2.2  | 185.3 |
| Rainfall (mm/week)        |          | 3.9±5.8  | 0    | 0.3  | 2.5  | 5.4  | 20.7  |
| Duration of sunshine (hours/week) | 4.7±2.4  | 0.1  | 3.0  | 4.5  | 6.3  | 11.0  |

P1, P25, P50, P75 and P99 are the 1st, 25th, 50th, 75th and 99th percentiles of variables, respectively. CO, carbon monoxide; PM, particulate matter; NO<sub>2</sub>, nitrogen dioxide; SO<sub>2</sub>, sulfur dioxide; TB, tuberculosis.

RESULTS

Basic characteristics of total patients with TB, air pollutants and meteorological factors

The distribution of weekly TB cases, air pollution and meteorological variables in Wuhan during 2014 to 2017 was summarised in table 1. In total, there were 25 077 TB cases. Among them, 140 (0.6%) were <15 years old, 17 533 (69.9%) were 15–59 years old and 7404 (29.5%) were ≥60 years old. There were 17 441 (69.5%) male and 7636 (30.5%) female TB cases. More than 75% observations of PM<sub>2.5</sub>, PM<sub>10</sub> and SO<sub>2</sub> were above WHO air quality guidelines and more than 50% observations of NO<sub>2</sub> were above the guidelines. The temporal variations of total TB cases and averaged air pollution concentrations and meteorological measurements over the study period showed a clear seasonality (online supplementary eFigures 2–3).

Lag associations between air pollution and initial TB outpatient visits

Lag-specific and cumulative ERs in initial outpatient TB cases for increased weekly concentrations of each air pollutant were shown for all ages combined over lag 0–16 weeks in single-pollutant models (figure 1 and online supplementary eTables 3–7). A 10 μg/m<sup>3</sup> increase in NO<sub>2</sub> was associated with 11.74% (95% CI: 0.70 to 23.98, lag 0–1 week) increase in initial TB consults. And a 10 μg/m<sup>3</sup> increase in SO<sub>2</sub> was associated with −19.00% (95% CI: −34.06 to −0.49, lag 0–9 weeks) to −22.23% (95% CI: −39.23 to −0.49, lag 0–16 weeks) increase in initial TB outpatient visits. There was no evidence on associations of PM<sub>10</sub>, PM<sub>2.5</sub> or CO with the risk of initial TB consults in the overall population.

On stratification by age, obviously different estimated exposure–response curves appeared between young (aged 15–59 years old) and old (≥60 years old) patients (figure 2 and online supplementary eTables 3–7). Among old patients, a 10 μg/m<sup>3</sup> increase in PM<sub>2.5</sub>, a 10 μg/m<sup>3</sup> increase in NO<sub>2</sub> and a 0.1 mg/m<sup>3</sup> increase in CO were associated with 17.38% (95% CI: 0.28 to 37.38, lag 0–16 weeks), 21.45% (95% CI: 1.44 to 45.41, lag 0–2 weeks) and 23.37% (95% CI: 0.94 to 50.8, lag 0–9 weeks) to 42.32% (95% CI: 1.16 to 100.22, lag 0–16 weeks) increases in initial TB consults, respectively.

Figure 1  (A) Lag-specific excess risks (%) and (B) cumulative excess risks (%) in total initial outpatient visits for TB per 10-unit increase in weekly mean concentrations of air pollution over lagged 16 weeks in single-pollutant models. CO, carbon monoxide; NO<sub>2</sub>, nitrogen dioxide; PM, particulate matter; SO<sub>2</sub>, sulfur dioxide; TB, tuberculosis.
Besides, cumulative ERs of SO₂ were from −18.4% (95% CI: −32.32 to −1.62, lag 0–7 weeks) to −28.65% (95% CI: −44.32 to −8.58, lag 0–16 weeks) among the young patients and −22.83% (95% CI: −39.72 to −1.21, lag 0–6 weeks) to −23.85% (95% CI: −41.79 to −0.37, lag 0–8 weeks) among the old patients.

Once stratified by gender, the pattern of association with NO₂ and SO₂ previously observed in the whole patients with TB only persisted in the male ones (figure 3 and online supplementary eTables 3–7). NO₂ had an immediate effect on TB cases at the same week with 12.8% (95% CI: 0.97 to 26.02, lag 0–1 week) increase in initial TB consults. In addition, reduced risks of SO₂ on TB cases were from −19.21% (95% CI: −33.66 to −1.6, lag 0–7 weeks) to −23.82% (95% CI: −41.31 to −1.11, lag 0–16 weeks).

When stratified by the season of TB incidence (online supplementary eFigure 4 and eTables 8–9), during September to February in next year, increased CO was positively associated with the risk of initial TB outpatient visits with cumulative ERs lasting from 44.54% (95% CI: 16.06 to 80.02, lag 0–1 week) to 201.9% (95% CI: 29.42 to 604.28, lag 0–16 weeks). Besides, increased PM₁₀ was associated with 4.64% (95% CI: 0.22 to 9.26, lag 0 week) increase in initial TB outpatient visits. But no significant cumulative effects of all the air pollutants were found during March to August, despite lag-specific effects of PM₁₀ at lag 6–8 weeks and NO₂ at lag 6 week.

In addition, we analysed the effects of air pollution on TB outpatient visits at daily level over lag 0–7, lag 0–14 and lag 0–21 days (online supplementary eTable 10 and eFigures 5–9), we only found that increased PM₂.₅ was associated with reduced risk of initial TB consults over lag 0–2 days among male patients, and increased SO₂ was associated with increased risk of initial TB consults over lag 7–14 days. There was no evidence on associations of PM₁₀, NO₂ or CO with the risk of initial TB consults in the total population and subgroups.

### Sensitivity analyses

The reasons and detailed results for sensitivity analyses were shown in the online supplementary files. In brief, despite some changes occurred in certain subgroups or pollutants, the main results were not substantially changed, when conducting the two-pollutant models (online supplementary eFigures 10–14), when excluding retreated TB cases (online supplementary eFigures 15–17) and when changing the max lags (online supplementary eFigure 18) and dfs for smoother time and meteorological factors (online supplementary eFigures 19–20).
DISCUSSION

Lag associations between air pollution and initial TB outpatient visits

Due to severe weather conditions and increased local emissions especially from its complex regional transport processes and recent rapid urbanisation construction in Wuhan, air pollution in this city is getting quite serious.\(^{16,17}\) This study conducted in Wuhan, to our knowledge, was the first to estimate the weekly lag associations of conventional air pollutants with the risk of initial TB outpatient visits in the world. In our study, the risk of total initial TB outpatient visits was positively associated with NO\(_2\) but inversely associated with SO\(_2\). On stratification by age, we observed positive associations of initial TB consults with PM\(_{2.5}\), NO\(_2\), and CO among old patients and inverse associations of initial TB consults with SO\(_2\) among both young and old ones. When stratified by sex, the associations of SO\(_2\) and NO\(_2\) previously shown in the total patients were only observed in the male ones. Given that our study was based on air pollution exposure at weekly level rather than acute exposure\(^{8,9}\) or long-term exposure\(^{14,15}\) reported in other studies, the results mainly revealed some susceptible populations for the risk of initial TB consults with the exposure to air pollutants at fluctuated levels, which, to some extent, implied subacute impact of air pollutants on the risk of initial TB consults. Furthermore, the results analysed using data at daily level also provided some evidences, as the strength of its correlation signal was weak in the daily DLNM.

As TB incubation period varies from weeks to years,\(^{18,19}\) it is difficult to distinguish the time of TB onset. However, there is a time interval between onset of symptoms and initial TB consults, defined as health-seeking delay, the medians of which reported in China were 2.5–7.5 weeks.\(^{10,11}\) Accordingly, the lag association between increased air pollution and subsequent initial TB consults reflected two stages: the time required for health-seeking delay and the development of \textit{M. tuberculosis} growth (the partial incubation period of TB). Furthermore, as the early \textit{M. tuberculosis} infection and its subsequent development are basically regulated by initial interaction between \textit{M. tuberculosis} and host immune response,\(^{19}\) significant short-lag effects of PM\(_{2.5}\) (lag 1–2 weeks), NO\(_2\) (lag 0–1 weeks) and CO (lag 3–5 weeks) observed in the subgroups may mainly refer to the former stage. During the stage, increased levels of air pollution may play a role in promoting inflammatory response in the development of \textit{M. tuberculosis} infection, thus leading to earlier patients’ initial health-seeking.

We found that NO\(_2\) was strongly associated with initial TB visits over lag 0–1 weeks. Similarly, other studies have previously reported significant short-interval lag effects of NO\(_2\) in TB outcomes, such as increased risk of active TB over lag 0–2 days\(^{6}\) and higher ORs for TB-related hospital admission at lag 1.5–2 weeks,\(^{20}\) which indicate that NO\(_2\) might play a ‘priming’ role in patients’ initial health-seeking due to TB symptoms. It is consistent with previous medical research, in which outdoor NO\(_2\) was demonstrated to impair airway mucous membranes and mucociliary clearance and may facilitate access of inhaled exogenous allergen into respiratory immune system and cause respiratory symptoms.\(^{21}\)

Despite the lag-specific effects of increased PM\(_{2.5}\), occurred in the old at lag 1–2 weeks, their significant cumulative effects could last for 4 months. You et al\(^{17}\) also revealed a stable association between increased PM\(_{2.5}\) during winter and increased number of TB cases in the subsequent spring or summer in Beijing and Hong Kong. Some toxicological experiments indicated that PM could suppress respiratory epithelium innate immunity,\(^{22,24}\) which may increase host’s susceptibility to early \textit{M. tuberculosis} infection and TB progression. But we did not find significant association between PM\(_{10}\) and TB outcome, which is consistent with some other studies.\(^{14,15,20}\) As particle size was reported to inversely correlate with PM toxicity in producing pulmonary inflammatory response,\(^{23}\) PM\(_{10}\) might be too coarse an indicator to detect the association between PM toxicity and TB visits.

Our study found positive associations between increased level of CO and initial TB consults lasted from over lag 0–9 weeks to lag 0–16 weeks. No previous study has found significant association between short-term or long-term exposure of CO and TB outcomes, except that Smith et al\(^{10}\) found a significant positive association between long-term exposure of CO and TB incidence in Northern California only in the single-pollutant model. The potential mechanisms between short-term or long-term exposure of CO and TB outcomes are still not clear. But an experiment in mice discovered a gradually decreased mRNA expression of several proinflammatory cytokines and cell signalling enzymes that implicated in controlling \textit{M. tuberculosis} infection when mice were exposed to diesel exhaust (measured including CO) from 1 to 6 months.\(^{36,37}\)

We observed increased SO\(_2\) was positively associated with increased risk of initial TB consults at lag 2 weeks in those ≥60 years old with no significant cumulative effects. But during various lagged weeks, we also found inverse associations of SO\(_2\) with initial TB outpatient visits among young patients, old patients and male ones, apart from the total patients. The adverse effects of SO\(_2\) may be related to its toxic effects by enhancing the inflammatory reaction in lungs.\(^{37}\) Previous studies showed positive associations of daily exposure to SO\(_2\) with TB,\(^{6,8}\) but a study at Ningbo in China also showed inverse associations between SO\(_2\) and the risk of initial TB outpatient visits using daily data.\(^{9}\) Despite its toxic effects of SO\(_2\) on many organs, its protective biological effects on TB have been observed in animal and cell experiments. In male mice, SO\(_2\) inhalation at 14 mg/m\(^3\) (5 ppm) increased levels of interleukin 6 (IL-6) and tumour necrosis factor \(\alpha\) (TNF-\(\alpha\)) in lungs as well as the level of TNF-\(\alpha\) in serum.\(^{28}\) IL-6 and TNF-\(\alpha\) are involved in immune cell differentiation and chemotaxis and granuloma formation, which is critical to control \textit{M. tuberculosis} infection.\(^{19}\) Furthermore, in vitro experiments have shown that exogenous SO\(_2\), by SO\(_2\)-releasing molecules, has a potency of inhibiting the growth of \textit{M. tuberculosis} higher than first-line antitubercular agent isoniazide.\(^{29}\) Due to inconsistent findings of the effects of SO\(_2\) on TB in population-based studies, more studies are required to clarify the effects.

Old patients were more susceptible to the exposure of PM\(_{2.5}\), NO\(_2\), and CO in the increased risk of initial TB consults. One plausible reason is that older people had a higher TB incidence contributed by reactivation of TB infection obtained decades earlier,\(^{30}\) and elevated concentrations of those air pollutants may aggravate their respiratory inflammation. Moreover, their particular susceptibility to TB development is potentially linked with low-grade systemic inflammation widespread among this group.\(^{31}\)

We also found the males had greater sensitivity to increased risk of initial TB consults when exposed to NO\(_2\) at a higher level, which may be attributable to their social and biological gender-related factors. For example, males are more likely to work in the circumstances such as chemical plants, coal miners and roads, which may expose men to more source of air pollutants.\(^{32}\) Furthermore, male sex hormones may play a part in their lower resistance to \textit{M. tuberculosis} infection, as the stimulated secretion of a series of cytokines, such as TNF, IL-2 or IL-10,
could be inhibited by testosterone but enhanced by 17β-oestradiol and downstream oestrogens. Additionally, in China there is a much higher prevalence of smoking in men (68.2%) than in women (11.7%). Some evidence has shown that smoking increased risk of developing TB. Smoking and air pollution may have interactive effects on TB incidence to some extent as nicotine or cigarette smoke could inhibit T cell-mediated immunity, which may explain males’ higher susceptibility to the progression to TB. But the potential mechanism why males had greater sensitivity to decreased risk of initial TB consults when exposed to higher level of SO₂ needs further research.

In addition, during September to February in the next year, significant positive association of increased risk of initial TB outpatient visits with increased CO and PM₁₀ were separately observed, especially the apparent effects of CO. They were mainly attributed to the stimulative effects to the respiratory system by CO and PM₁₀ in high concentrations during this period, since the mean concentrations of CO and PM₁₀ were separately 1.24 mg/m³ and 79.65 μg/m³ during this period whereas those of CO and PM₁₀ were 0.95 mg/m³ and 49.49 μg/m³ during March to August, respectively. Additionally, meteorological factors, such as temperature and humidity, were known to affect air pollution concentrations.

Implications of public health
In summary, we applied an ecological design discovering associations between incremental level of some air pollutants and the risk of initial TB outpatient visits instead of exploring a causal relationship. The effects of weekly increased level of air pollution on the risk of initial TB consults may be underestimated since the maximum lag period can be as long as 4 months, and it also warrants caution to interpret effects of air pollution on TB incidence. Using a DLNM at daily level seems to lose more information than that at weekly level, as we did not observe acute effects of air pollutants on the risk of initial TB consults and there is a limit in max lag days in DLNM using daily data. The risk prediction models of initial TB consults by assessing current status of air pollution are useful for public health personnel to improve TB screening strategies on high polluted period and offer more TB medical assistance in high-polluted areas. In addition, reducing levels of PM₁₀, NO₂ and CO in air could also help TB prevention and control in population.

Strengths and limitations
A key advance of this study is that we used weekly data to explore effects of air pollution, which will help further understand impacts of fluctuated levels of air pollution in the process of outpatient visits for patients with TB over 4 months. Second, DLNM can simultaneously represent the exposure–response relationship with the predictor variable and the lag–response relationship with the lag time, instead of only estimating effects of a single lag or several days at a particular lag as in other models. However, several limitations of our study should be addressed. First, our study was limited to only one city with relatively shorter research periods, which may limit the generalisation of our results to other cities. Considering Wuhan is the largest city in Central China, where outdoor air pollution was at an intermediate or upper level, and its epidemic situation of TB was close to the national average level, our study can be representative of some cities in China. Furthermore, larger studies including different parts of China with longer periods in the future are needed. Second, our analyses were based on data at an aggregate level and failed to get information on personal risk factors for stratification, which implicates the potential to introduce information bias and confounders to our results.

CONCLUSIONS
Our findings interpreted the associations of air pollutants including PM₁₀, CO, NO₂ and SO₂ with the risk of initial TB consults over lagged 16 weeks with the DLNM using weekly data. Old patients were sensitive to PM₁₀, CO and NO₂ and male ones were sensitive to NO₂ and SO₂ with significant lag effects at various lag weeks. The findings implied that effects of air pollution on initial TB consults may be involved in the development of M. tuberculosis growth and patient health-seeking delay.

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Contributors
MX, JL, HC and PH: study concept and design; HC: data collection and supervision; MX: drafting of the manuscript; MX and JL: analysis and interpretation of data; HC, JH, YZ, BI, LX, RC and PH: involved in the critical revision of the manuscript for important intellectual content; PY, YZ and JH: statistical analysis; RC: polishing the language.

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