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 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 nonlinear 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/m^3 increase in NO_2 was associated with 11.74% (95% CI: 0.70-23.98, lag 0-1 weeks), 21.45% (1.44-45.41, lag 0-2) and 12.8% (0.97-26.02, lag 0-1) increase in initial TB consults among all TB patients, old patients (≥60 years old) and male ones, respectively. A 10 μg/m^3 increase in SO_2 was associated with -22.23% (-39.23 to -0.49, lag 0-16), -28.65% (-44.3 to -8.58, lag 0-16), -23.85 (-41.79 to -0.37, lag 0-8), and -23.82% (95% CI: -41.31 to -1.11, lag 0-16) increase in initial TB consults among the total, young (aged 15-59 years old), old and male patients, respectively. In old patients, a 0.1 mg/m^3 increase in CO and a 10 μg/m^3 increase in $PM_{2.5}$ were separately associated with 42.32% (1.16-100.22, lag 0-16) and 17.38% (0.28-37.38, lag 0-16) 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.

Key words: Tuberculosis; Initial outpatient visits; Air pollution

Key messages

What is already known about this subject?

- Previous epidemiological and toxicological studies have revealed the association between ambient air pollution and the development of *Mycobacterium tuberculosis* infection. Data is lacking on the association between air pollution and initial TB outpatient visits with short-interval data.

What are the new findings?

- Our study revealed that the risk of initial TB consults was positively associated with increased levels of $PM_{2.5}$, CO and NO_2 and was inversely associated with increased level of SO_2 over lagged 16 weeks.
- Old patients were sensitive to $PM_{2.5}$, CO, NO_2 and SO_2 and the male ones were sensitive to NO_2 and SO_2 with significant lag effects at various lag weeks.

How might this impact on policy or clinical practice in the foreseeable future?

- The weekly lag effects of air pollution on TB consults have important implication for TB prevention and control in population. It will help policymakers improve TB screening strategies on high polluted period and offer more TB medical assistance in high polluted areas.

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 TB patients in the world.[1] TB is caused by the bacterium *Mycobacterium tuberculosis* (*M.tb*). Individuals with suppressed host immune system conditions, such as human immunodeficiency virus 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- and population-based studies reported the association of TB cases with long-term air pollution exposure. In view of individual two-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 (NO_2) 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.[5] A study conducted by Hwang SS *et al* [6] in South Korea found a positive association of sulfur dioxide (SO_2) 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.[7-9] Analyzing monthly data, You *et al* [7] observed a stable link between incremental aerodynamic diameter of ≤ 2.5 μm ($PM_{2.5}$) concentration and increase in TB cases. Using daily data, Zhu *et al* [8] found that increased level of NO_2 and SO_2 positively and independently correlated with newly reported TB cases, while Ge's group reported an inverse association of SO_2 exposure with initial TB outpatient visits. [9]

The current epidemiological studies have suggested associations between air pollution and initial *M.tb* 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 TB patients are often accompanied by chronic symptoms for several weeks before their initial outpatient visits [10 11] 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 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 (center: 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 square kilometers with a permanent population of 10.914 million at the end of 2017. [12]

Data on TB outpatients

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 Wuhan Tuberculosis Institution. We also collected demographic information of each TB case, including age, sex and dates of initial TB outpatient visits. In 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.[8] 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://106.37.208.233:20035), 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 (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 nonlinear model (DLNM)

As distributed lag nonlinear model (DLNM) can reveal the additional lag dimension of the exposure-response relationship,[13] 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 $Y_t \mid \mu_t \sim POI(\mu_t)$, where μ_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:

$$
\begin{aligned}
Log(\mu_t) &= \alpha + \beta AP_{t,l} + ns(temp,3) + ns(humidity,3) + ns(wind,3) + ns(sunshine,3) \\
&\quad + \lambda year + ns(time,6) + \delta Spring\text{-}festival \qquad (1) \\
&= \alpha + \beta AP_{t,l} + COVs
\end{aligned}
$$

where α is the intercept, and $AP_{t,l}$ is the cross-basis matrix by using a double natural cubic spline DLNM to each indicator of air pollution (AP); β is the coefficient for $AP_{t,l}$, and l is the maximum lag time up to 16 weeks; λ and δ 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 degrees of freedom (df), which was determined based on the model fit using Akaike's information criterion (AIC).[14] We fitted natural cubic splines with a priori 3 df to control for meteorological variables as covariates.[8] 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 supplementary materials (Section 2, including eTables 1-2,).

We used excess risk (ER) estimates, which represented as the percentage change in initial TB outpatient visits per 10 units 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 were 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. [9] 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 ,[15] 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, including eTable 10) .Finally, we conducted several sensitivity analyses to assess the robustness of our main results by: (1) fitting two-pollutant models, (2) excluding 1,331(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) .

RESULTS

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

The distribution of weekly TB cases, air pollution and meteorological variables in Wuhan during 2014 to 2017 was summarized 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 7,404 (29.5%) were ⩾ 60 years old. There were 17,441(69.5%) male and 7,636 (30.5%) female TB cases. More than 75% observations of $PM_{2.5}$, PM_{10} and SO_2 were above WHO air quality guidelines and more than 50% observations of NO_2 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 (eFigure 2-3).

Table 1

Summarized statistics of weekly TB cases , air pollution and meteorological variables in Wuhan, 2014-2017(n = 25,077).

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	0.7 ± 0.9	0	0	0	1	3
Young, 15-59	83.9 ± 18.4	34	72	83	96	127
Middle and old, ≥60	35.4 ± 9.6	12	31	35	41	62
Pollutant concentration						
$PM_{2.5}$ (μg/m^3)	64.9 ± 35.7	17.0	41.0	56.0	84.0	178.6
PM_{10} (μg/m^3)	101.2± 40.6	32.6	70.0	97.0	123.0	210.1
SO_2(μg/m^3)	18.5 ± 12.7	4.0	9.0	16.0	23.0	71.9
NO_2 (μg/m^3)	49.7 ± 15.4	25.2	38.0	48.0	57.0	93.9
CO (mg/m^3)	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 (hr/week)	4.7 ± 2.4	0.1	3.0	4.5	6.3	11.0

Note: SD: standard deviation; P1, P25, P50, P75, and P99 are the 1st, 25th, 50th, 75th and 99th percentiles of variables, respectively.

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 eTables 3-7). A 10 μg/m^3 increase in NO_2 was associated with 11.74% (95% CI: 0.70-23.98, lag 0-1) increase in initial TB consults. And, a 10 μg/m^3 increase in SO_2 was associated with -19.00% (95% CI: -34.06 to - 0.49, lag 0-9) to -22.23% (95% CI: -39.23 to -0.49, lag 0-16) increase in initial TB outpatient visits. There was no evidence on associations of PM_{10}, $PM_{2.5}$ or CO with the risk of initial TB consults in the overall population.

Upon 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 eTables 3-7). Among old patients, a 10 μg/m^3 increase in $PM_{2.5,}$ a 10 μg/m^3 increase in NO_2 and a 0.1 mg/m^3 increase in CO were associated with 17.38% (95% CI: 0.28, 37.38, lag 0-16) , 21.45% (95% CI: 1.44, 45.41, lag 0-2) and 23.37% (95% CI: 0.94, 50.8, lag 0-9) to 42.32% (95% CI: 1.16, 100.22, lag 0-16) increases in initial TB consults, respectively. Besides, cumulative ERs of SO_2 were from -18.4% (95% CI: -32.32,-1.62, lag 0-7) to -28.65% (95% CI: -44.32 to -8.58, lag 0-16) among the young patients and -22.83% (95% CI: -39.72 to -1.21, lag 0-6) to -23.85 (95% CI: -41.79 to -0.37, lag 0-8) among the old patients.

Once stratified by gender, the pattern of association with NO_2 and SO_2 previously observed in the whole TB patients only persisted in the male ones (Figure 3 and eTables 3-7). NO_2 had an immediate effect on TB cases at the same week with 12.8% (95% CI: 0.97, 26.02, lag 0-1) increase in initial TB consults. In addition, reduced risks of SO_2 on TB cases were from -19.21% (95% CI: -33.66 to -1.6, lag 0-7) to -23.82% (95% CI: -41.31 to -1.11, lag 0-16).

When stratified by the season of TB incidence (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, 80.02, lag 0-1) to 201.9% (95%CI: 29.42, 604.28, lag 0-16). Besides, increased $PM_{2.5}$ was associated with 4.64% (95%CI: 0.22, 9.26, lag 0) 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 PM_{10} at lag 6-8 weeks and NO_2 at lag 6 week.

In addition, we analyzed the effects of air pollution on TB outpatient visits at daily level over lag 0-7, lag 0-14 and lag 0-21 days (eFigures 5-9), we only found that increased $PM_{2.5}$ was associated with reduced risk of initial TB consults over lag 0-2 days among male patients, and increased SO_2 was associated with increased risk of initial TB consults over lag 7-14 days. There was no evidence on associations of PM_{10}, NO_2 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 supplementary materials. In brief, despite some changes occurred in certain subgroups or pollutants, the main results were not substantially changed, when conducting the two-pollutant models (eFigures 10-14), when excluding retreated TB cases (eFigures 15-17), and when changing the max lags (eFigure 18) and dfs for smoother time and meteorological factors (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 urbanization 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 time 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. Upon 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 [3 4] 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 sub-acute impact of air pollutants on the risk of initial TB consults. Furthermore, the results analyzed 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] it's 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 *M.tb* growth (the partial incubation period of TB). Furthermore, as the early *M.tb* infection and its subsequent development are basically regulated by initial interaction between *M.tb* 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 *M.tb* 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 [8] and higher odds ratios 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 four months. You *et al* [7] 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 *M.tb* infection and TB progression. But we did not find significant association between PM_{10} and TB outcome, which is consistent with some other studies.[3 4 6 20] As particle size was reported to inversely correlate with PM toxicity in producing pulmonary inflammatory response,[25] 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- or long-term exposure of CO and TB outcomes, except that Smith *et al* [4] 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- or long-term exposure of CO and TB outcomes is still not clear. But an experiment in mice discovered a gradually decreased mRNA expression of several proinflammatory cytokines and cell signaling enzymes that implicated in controlling *M.tb* infection when mice were exposed to diesel exhaust (measured including CO) from one to six months.[26]

We observed increased SO_2 was positively associated with increased risk of initial TB consults at lag 2 week 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.[27] 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 IL-6 and TNF-α in lungs as well as the level of TNF-α in serum.[28] IL-6 and TNF-α are involved in immune cell differentiation and chemotaxis and granuloma formation, which is critical to control *M.tb* infection.[19] Furthermore, vitro experiments have shown that exogenous SO_2, by SO_2-releasing molecules, has a potency of inhibiting the growth of *M.tb* 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 are 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 *M.tb* 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 17 β-estradiol (E2) and downstream estrogens.[33] Additionally, in China there is a much higher prevalence of smoking in men (68.2%) than women (11.7%).[34] Some evidence has shown that smoking increased risk of developing TB.[35 36] 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,[37] 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 SO_2 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

$PM_{2.5}$ were separately observed, especially the apparent effects of CO. They were mainly attributed to the stimulative effect to the respiratory system by CO and $PM_{2.5}$ in high concentrations during this period,since the mean concentrations of CO and $PM_{2.5}$ were separately 1.24 mg/m^3 and 79.65 μg/m^3 during this peroid whereas those of CO and PM2.5 were 0.95 mg/m^3 and 49.49 μg/m^3 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 four 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 is 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 $PM_{2.5}$, NO_2 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 TB patients over 4 months. Secondly, DLNM can simultaneously represent the exposure-response relationship with the predictor variable and the lag-response relationship with the lag time,[13] instead of only estimating effects of a single lag or several days at a particular lag as in other models.[38 39] However, several limitations of our study should be addressed. Firstly, our study was limited to only one city with relatively shorter research periods, which may limit the generalization 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,[40] 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. Secondly, 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 $PM_{2.5}$, CO, NO_2 and SO_2 with the risk of initial TB consults over lagged 16 weeks with the DLNM using weekly data. Old patients were sensitive to $PM_{2.5,}$ CO, and NO_2 and male ones were sensitive to NO_2 and SO_2 with significant lag effects at various lag weeks. The findings implied effects of air pollution on initial TB consults may be involved in the development of *M.tb* growth and patient health-seeking delay.

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Ethics approval None. All patients' personal data acquired were anonymous and did not contain any identifiable information, thus did not need patient consent.

Data sharing No additional data are available.

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Supplementary Materials

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

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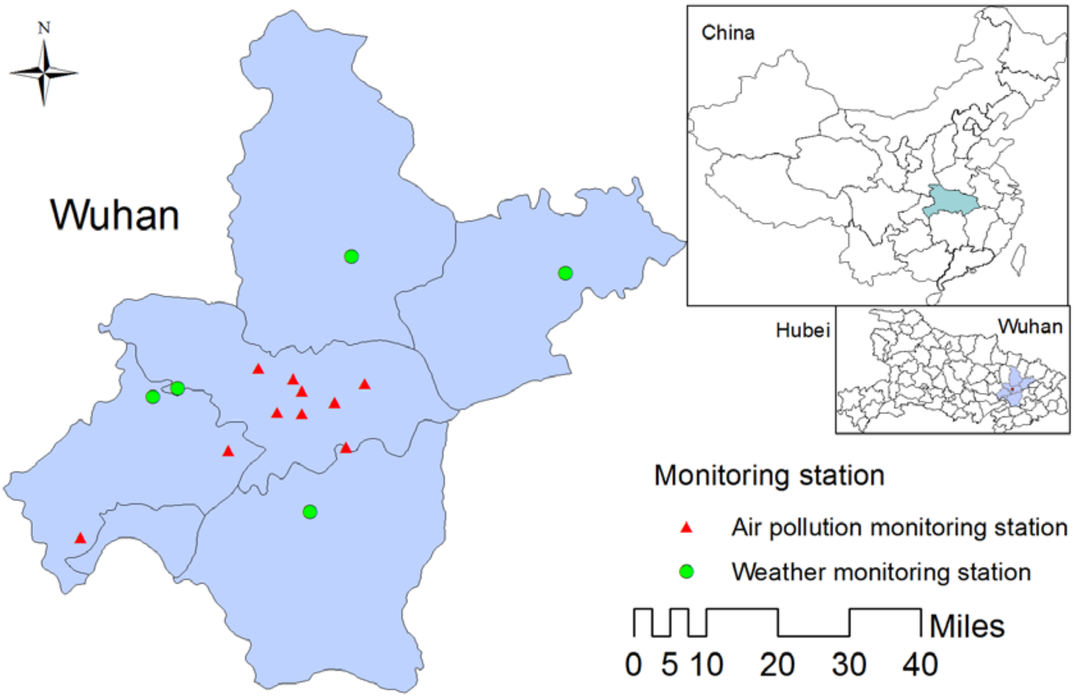
References

Section 1. Monitoring stations and trend plots



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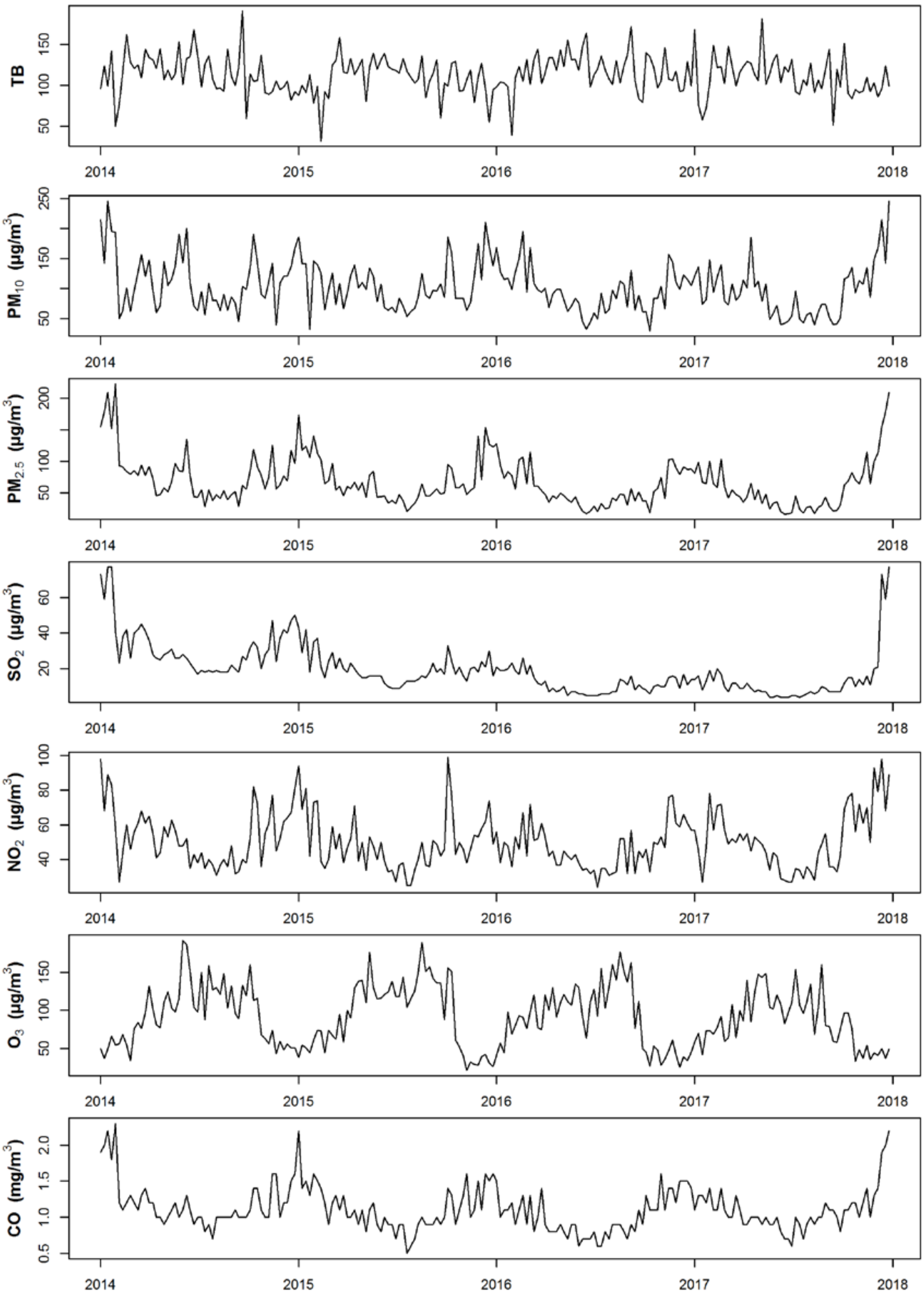

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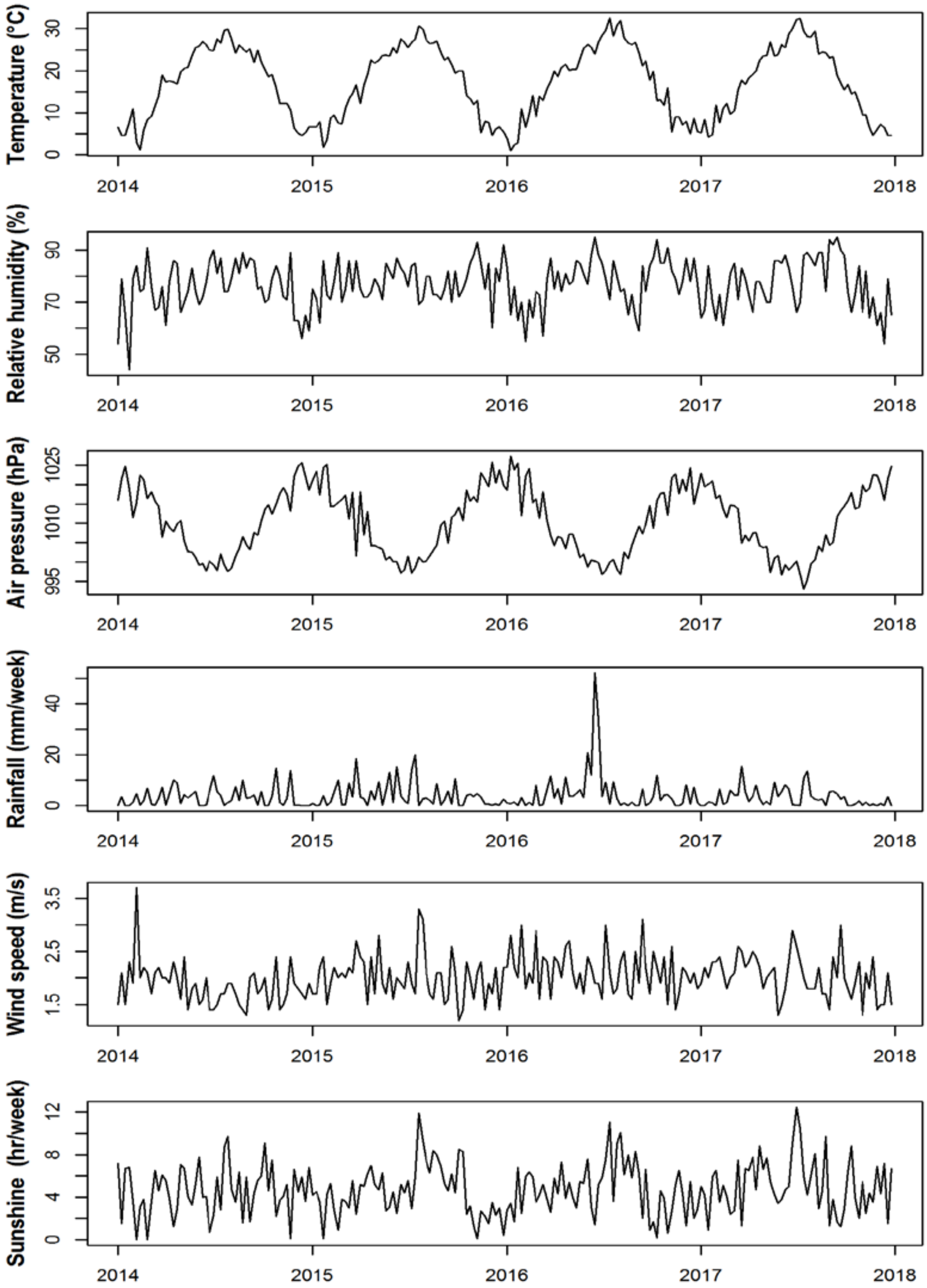


eFigure 3. Trend plot of weekly mean climate measures in Wuhan during the study period.

Section 2. Distributed lag nonlinear model (DLNM)

We fitted a DLNM model 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 $Y_t \mid \mu_t \sim POI(\mu_t)$, where μ_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:

$$
\begin{aligned}
Log(\mu_t) &= \alpha + \beta AP_{t,l} + \mathrm{ns}(temp,3) + \mathrm{ns}(humidity,3) + \mathrm{ns}(wind,3) + \mathrm{ns}(sunshine,3) \\
&\quad + \lambda \mathrm{year} + \mathrm{ns}(time,6) + \delta Spring\text{-}festival \qquad (1) \\
&= \alpha + \beta AP_{t,l} + \mathrm{COVs}
\end{aligned}
$$

where α is the intercept, and $AP_{t,l}$ is the cross-basis matrix by using a DLNM to each indicator of air pollution (AP). β is the coefficient for $AP_{t,l}$, l is the lag weeks. The rest meteorological factors and time variables in equation (1) are all covariates. λ and δ 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 used for controlling for the temporal autocorrelations with 6 degrees of freedom (df), which was determined based on the model fit using Akaike’s information criterion (AIC).[1] We added the *Spring-festival* term to control for the holiday effect. In China, people gather, particularly family members and friends (called union) to celebrate Chinese new year, called as Spring Festival , which would always lead to heath care seeking delay [2]. Thus, during the Spring Festival the consultation rate is relatively low. [2] We fitted natural cubic splines with a priori 3 df to control for meteorological variables. [3] As strong correlations between temperature and air pressure ($r = -0.94$) and between relative humidity and rainfall ($r = 0.73$) were observed in the initial analysis (see eTable 1), air pressure and rainfall were excluded from the final models to avoid collinearity.

To fully capture the overall impact of pollution and consider any potential harvesting effects, a lag of up to 16 weeks was used for pollution models. We chose 16 weeks based on the reported potential delayed periods of air pollution on TB cases lasting 3 to 6 months, [4] AIC and considerations of easy interpretation with not very long lags from an epidemiological perspective. [5] Then, we used a double natural cubic spline DLNM in which we fitted the natural cubic spline function to model both the nonlinear pollution effects and the lag effects. We set the medians of each pollutant concentration as reference values to calculate excess risks (%). We placed spline knots at equally spaced percentiles of pollution concentrations to allow sufficient flexibility at both ends of pollution concentration distribution; similarly, we laid spline knots at equally spaced $\log_{10}$-value scale of lags so that enough lag effects were allowed at shorter lag periods. [5] In order to build the best combination of the cross-basis function of air pollution and the lag in the two natural cubic splines, the optimal number of knots for each dimension was chosen on the basis of the smallest quasi-AIC(QAIC) [1 6] (see eTable 2).

eTable 1

Spearman’s correlation coefficients between weekly air pollution and meteorological variables in Wuhan, 2014–2017.

	$PM_{2.5}$	PM_{10}	SO_2	NO_2	CO	Temp	Humi	Press	Rain	Wind	Sun
$PM_{2.5}$	1	0.83[a]	0.74[a]	0.75[a]	0.81[a]	-0.7[a]	-0.44[a]	0.68[a]	-0.46[a]	-0.21[b]	-0.12
PM_{10}		1	0.63[a]	0.79[a]	0.58[a]	-0.43[a]	-0.65[a]	0.46[a]	-0.58[a]	-0.28[a]	0.24[b]
SO_2			1	0.57[a]	0.57[a]	-0.48[a]	-0.43[a]	0.49[a]	-0.35[a]	-0.25[a]	-0.02
NO_2				1	0.68[a]	-0.6[a]	-0.47[a]	0.6[a]	-0.47[a]	-0.38[a]	0.06
CO					1	-0.69[a]	-0.1	0.62[a]	-0.25[a]	-0.19	-0.32[a]
Temperature						1	0.22[b]	-0.94[a]	0.24[b]	-0.07	0.4[a]
Humidity							1	-0.31[a]	0.73[a]	0.01	-0.61[a]
Pressure								1	-0.38[a]	0.01	-0.27[a]
Rainfall									1	0.27[a]	-0.45[a]
Wind										1	-0.07
Sunshine											1

PM_{10}: particulate matter < 10 μm in aerodynamic diameter; $PM_{2.5}$: particulate matter < 2.5 μm in aerodynamic diameter; NO_2: nitrogen dioxide; CO: carbonic oxide.

[a] $P < 0.001$.

[b] $P < 0.05$.

eTable 2

Knots in the double natural cubic splines for the best model fitting in the distributed lag nonlinear model for each pollution model.

Model	Air Pollution	Lag (weeks)	Knots for the predictors	Knots for the lags
Model 1	PM_{10}	16	2	3
Model 2	$PM_{2.5}$	16	2	3
Model 3	NO_2	16	3	2
Model 4	CO	16	2	3

Section 3. Single-pollutant models in total population and subgroups

eTable 3

Lag-specific percentage changes (excess risk with 95% confidence interval) in initial outpatient visits for TB per 10 μg/m^3 increase in weekly mean concentrations of PM_{10} over lagged 16 weeks in single-pollutant models.

Lag (week)	All	15-59 years old	≥ 60 years old	Male	Female
0	-0.31(-2.05,1.46)	-0.6(-2.34,1.16)	0.21(-2.39,2.87)	-0.68(-2.5,1.18)	0.6(-1.83,3.1)
1	-0.47(-1.62,0.7)	-0.61(-1.76,0.56)	-0.03(-1.76,1.72)	-0.83(-2.04,0.39)	0.3(-1.32,1.95)
2	-0.54(-1.72,0.66)	-0.58(-1.76,0.61)	-0.36(-2.17,1.48)	-0.89(-2.13,0.37)	0.11(-1.59,1.85)
3	-0.45(-1.62,0.73)	-0.49(-1.66,0.69)	-0.67(-2.26,0.95)	-0.77(-2,0.47)	0.09(-1.41,1.61)
4	-0.29(-1.31,0.74)	-0.38(-1.4,0.66)	-0.59(-2.32,1.16)	-0.58(-1.65,0.51)	0.15(-1.48,1.79)
5	-0.14(-1.07,0.8)	-0.27(-1.2,0.67)	-0.26(-1.77,1.27)	-0.4(-1.38,0.59)	0.23(-1.18,1.66)
6	-0.02(-0.92,0.89)	-0.18(-1.08,0.73)	0.08(-1.23,1.4)	-0.25(-1.19,0.71)	0.31(-0.9,1.54)
7	0.08(-0.82,0.98)	-0.11(-0.99,0.79)	0.34(-0.89,1.58)	-0.12(-1.06,0.82)	0.37(-0.77,1.52)
8	0.15(-0.73,1.03)	-0.05(-0.92,0.82)	0.52(-0.67,1.73)	-0.03(-0.94,0.9)	0.41(-0.7,1.52)
9	0.2(-0.64,1.04)	0(-0.83,0.83)	0.64(-0.5,1.8)	0.05(-0.83,0.93)	0.43(-0.64,1.5)
10	0.23(-0.55,1.01)	0.03(-0.74,0.81)	0.71(-0.37,1.79)	0.1(-0.71,0.93)	0.43(-0.57,1.44)
11	0.25(-0.46,0.95)	0.06(-0.64,0.76)	0.72(-0.26,1.7)	0.14(-0.6,0.89)	0.42(-0.48,1.34)
12	0.25(-0.38,0.88)	0.07(-0.55,0.7)	0.69(-0.17,1.56)	0.17(-0.49,0.83)	0.4(-0.4,1.21)
13	0.24(-0.33,0.82)	0.08(-0.49,0.66)	0.63(-0.15,1.42)	0.18(-0.42,0.79)	0.38(-0.35,1.11)
14	0.22(-0.34,0.79)	0.09(-0.48,0.66)	0.55(-0.24,1.33)	0.19(-0.41,0.78)	0.34(-0.38,1.08)
15	0.2(-0.42,0.83)	0.09(-0.53,0.71)	0.44(-0.45,1.34)	0.18(-0.47,0.84)	0.3(-0.53,1.14)
16	0.18(-0.55,0.92)	0.09(-0.64,0.83)	0.33(-0.75,1.43)	0.18(-0.59,0.96)	0.26(-0.75,1.29)

eTable 4

Lag-specific percentage changes (excess risk with 95% confidence interval) in initial outpatient visits for TB per 10 μg/m^3 increase in weekly mean concentrations of $PM_{2.5}$ over lagged 16 weeks in single-pollutant models.

Lag (week)	All	15-59 years old	≥ 60 years old	Male	Female
0	0.71(-1.91,3.41)	-0.62(-2.75,1.56)	1.94(-1.03,5)	-0.47(-2.74,1.86)	2.01(-1.26,5.39)
1	-0.1(-1.42,1.23)	-0.12(-1.2,0.96)	**1.74(0.26,3.25)**	0.19(-0.96,1.34)	0.01(-1.62,1.67)
2	-0.13(-1.71,1.48)	0.17(-0.86,1.21)	**1.54(0.12,2.98)**	0.57(-0.53,1.68)	-0.42(-2.37,1.56)
3	0.59(-0.44,1.63)	0.12(-0.94,1.2)	1.32(-0.15,2.81)	0.51(-0.63,1.66)	0.71(-0.57,2.01)
4	0.77(-0.42,1.98)	-0.09(-0.99,0.81)	1.12(-0.12,2.37)	0.22(-0.74,1.19)	1.17(-0.31,2.68)
5	0.47(-0.53,1.49)	-0.28(-1.11,0.55)	0.95(-0.18,2.09)	-0.02(-0.9,0.86)	0.91(-0.34,2.17)
6	0.13(-0.73,1)	-0.41(-1.24,0.44)	0.82(-0.32,1.97)	-0.19(-1.08,0.71)	0.51(-0.55,1.59)
7	-0.1(-0.97,0.77)	-0.47(-1.34,0.4)	0.72(-0.46,1.92)	-0.28(-1.2,0.66)	0.21(-0.86,1.29)
8	-0.24(-1.15,0.68)	-0.49(-1.37,0.4)	0.65(-0.55,1.87)	-0.3(-1.24,0.66)	-0.02(-1.13,1.11)
9	-0.29(-1.22,0.65)	-0.46(-1.34,0.43)	0.61(-0.58,1.82)	-0.26(-1.19,0.69)	-0.17(-1.31,0.99)
10	-0.27(-1.18,0.66)	-0.39(-1.24,0.47)	0.6(-0.56,1.77)	-0.16(-1.07,0.75)	-0.26(-1.38,0.88)
11	-0.18(-1.05,0.71)	-0.28(-1.1,0.54)	0.6(-0.52,1.73)	-0.03(-0.9,0.86)	-0.29(-1.37,0.8)
12	-0.03(-0.87,0.82)	-0.15(-0.96,0.67)	0.62(-0.49,1.74)	0.15(-0.72,1.02)	-0.28(-1.32,0.77)
13	0.16(-0.7,1.02)	0.01(-0.84,0.87)	0.65(-0.51,1.83)	0.36(-0.55,1.27)	-0.24(-1.3,0.83)
14	0.38(-0.57,1.33)	0.18(-0.77,1.14)	0.69(-0.6,2.01)	0.59(-0.43,1.61)	-0.17(-1.34,1.02)
15	0.62(-0.5,1.75)	0.37(-0.74,1.49)	0.74(-0.76,2.27)	0.83(-0.35,2.03)	-0.08(-1.46,1.33)
16	0.88(-0.48,2.25)	0.56(-0.74,1.88)	0.8(-0.97,2.59)	1.09(-0.3,2.5)	0.02(-1.65,1.72)

Note: Values were percentage increase (%) and 95% CI in risk of outpatient visits for TB.
The bold means statistically significant ($P < 0.05$).

eTable 5

Lag-specific percentage changes (excess risk with 95% confidence interval) in initial outpatient visits for TB per 10 μg/m^3 increase in weekly mean concentrations of SO_2 over lagged 16 weeks in the single-pollutant models.

Lag (week)	All	15-59 years old	≥ 60 years old	Male	Female
0	-1.81(-11.15,8.52)	-1.69(-11.04,8.64)	-15.01(-27.91,0.2)	-4.72(-14.21,5.82)	5.07(-7.55,19.41)
1	-2.04(-6.38,2.5)	-2.21(-6.55,2.32)	4.09(-2.89,11.58)	-2.85(-7.38,1.89)	-0.3(-5.87,5.6)
2	-2.22(-5.86,1.56)	-2.6(-6.22,1.15)	**8.97(0.24,18.46)**	-1.65(-5.51,2.37)	-3.69(-8.2,1.04)
3	-2.31(-6.18,1.71)	-2.78(-6.61,1.21)	-3.03(-7.93,2.13)	-1.58(-5.68,2.69)	-4.18(-8.97,0.86)
4	-2.33(-5.36,0.81)	-2.8(-5.81,0.31)	**-8.13(-13.46,-2.47)**	-2.1(-5.3,1.2)	-3.11(-6.92,0.86)
5	-2.29(-4.73,0.22)	**-2.76(-5.19,-0.26)**	**-6.61(-10.95,-2.07)**	-2.53(-5.1,0.1)	-2.02(-5.14,1.19)
6	-2.2(-4.47,0.13)	**-2.68(-4.94,-0.35)**	**-3.78(-7.12,-0.33)**	**-2.76(-5.14,-0.33)**	-1.22(-4.14,1.78)
7	-2.07(-4.35,0.27)	**-2.56(-4.83,-0.23)**	-1.51(-4.65,1.72)	**-2.81(-5.19,-0.37)**	-0.69(-3.63,2.34)
8	-1.9(-4.18,0.44)	**-2.41(-4.68,-0.08)**	0.2(-3.09,3.6)	**-2.69(-5.06,-0.25)**	-0.4(-3.34,2.64)
9	-1.69(-3.89,0.55)	-2.22(-4.41,0.02)	1.39(-1.99,4.89)	**-2.42(-4.71,-0.07)**	-0.32(-3.15,2.59)
10	-1.46(-3.48,0.61)	-2.01(-4.03,0.05)	2.11(-1.16,5.49)	-2.02(-4.14,0.15)	-0.44(-3.03,2.23)
11	-1.2(-3.02,0.66)	-1.78(-3.6,0.07)	2.42(-0.56,5.49)	-1.51(-3.42,0.44)	-0.71(-3.04,1.67)
12	-0.91(-2.62,0.83)	-1.53(-3.24,0.21)	2.38(-0.28,5.12)	-0.9(-2.71,0.94)	-1.13(-3.29,1.09)
13	-0.61(-2.46,1.28)	-1.26(-3.11,0.61)	2.07(-0.54,4.75)	-0.21(-2.17,1.78)	-1.64(-3.95,0.72)
14	-0.29(-2.57,2.05)	-0.98(-3.26,1.34)	1.56(-1.52,4.72)	0.53(-1.89,3.02)	-2.24(-5.06,0.67)
15	0.04(-2.9,3.06)	-0.7(-3.61,2.31)	0.9(-3.08,5.05)	1.33(-1.81,4.56)	-2.88(-6.48,0.85)
16	0.37(-3.34,4.22)	-0.4(-4.09,3.42)	0.19(-4.94,5.6)	2.14(-1.83,6.28)	-3.55(-8.04,1.16)

Note: Values were percentage increase (%) and 95% CI in risk of outpatient visits for TB.

The bold means statistically significant ($P < 0.05$).

eTable 6

Lag-specific percentage changes (excess risk with 95% confidence interval) in initial outpatient visits for TB per 10 μg/m^3 increase in weekly mean concentrations of NO_2 over lagged 16 weeks in single-pollutant models.

Lag (week)	All	15-59 years old	≥ 60 years old	Male	Female
0	**7.85(0.86,15.32)**	5.88(-1.03,13.27)	**12.45 (2.59, 23.25)**	**8.39(0.93,16.4)**	2.6(-3.22,8.77)
1	3.61(-0.81,8.22)	2.54(-1.87,7.14)	**6.16 (0,12.71)**	4.07(-0.67,9.03)	0.25(-3.34,3.99)
2	0.5(-4.03,5.25)	0.02(-4.53,4.78)	1.74(-4.48,8.36)	0.84(-4.02,5.95)	-1.29(-4.86,2.41)
3	-0.92(-5.18,3.54)	-1.26(-5.55,3.22)	-0.06(-5.89,6.13)	-0.76(-5.33,4.02)	-1.58(-5.09,2.06)
4	-1.33(-4.68,2.15)	-1.76(-5.13,1.73)	-0.35(-4.95,4.47)	-1.36(-4.95,2.36)	-1.18(-4.24,1.99)
5	-1.5(-4.27,1.35)	-2.02(-4.8,0.84)	-0.39(-4.2,3.57)	-1.67(-4.63,1.37)	-0.75(-3.62,2.21)
6	-1.6(-4.18,1.06)	-2.16(-4.76,0.5)	-0.43(-3.99,3.26)	-1.85(-4.6,0.99)	-0.43(-3.31,2.54)
7	-1.63(-4.22,1.04)	-2.2(-4.8,0.47)	-0.46(-4.03,3.24)	-1.9(-4.66,0.94)	-0.2(-3.14,2.83)
8	-1.59(-4.22,1.1)	-2.13(-4.76,0.57)	-0.49(-4.11,3.26)	-1.83(-4.63,1.04)	-0.07(-3.02,2.97)
9	-1.51(-4.11,1.17)	-1.98(-4.59,0.7)	-0.52(-4.1,3.2)	-1.67(-4.45,1.19)	-0.01(-2.89,2.96)
10	-1.37(-3.9,1.22)	-1.75(-4.29,0.86)	-0.54(-4.02,3.06)	-1.42(-4.12,1.36)	-0.02(-2.78,2.81)
11	-1.2(-3.64,1.3)	-1.46(-3.91,1.06)	-0.56(-3.91,2.9)	-1.09(-3.71,1.59)	-0.09(-2.69,2.58)
12	-0.99(-3.4,1.49)	-1.11(-3.54,1.39)	-0.58(-3.88,2.83)	-0.7(-3.3,1.96)	-0.21(-2.69,2.34)
13	-0.75(-3.29,1.85)	-0.71(-3.28,1.92)	-0.6(-4.05,2.97)	-0.26(-2.99,2.55)	-0.37(-2.85,2.18)
14	-0.49(-3.35,2.45)	-0.29(-3.18,2.7)	-0.62(-4.48,3.4)	0.22(-2.86,3.4)	-0.55(-3.22,2.18)
15	-0.22(-3.58,3.26)	0.17(-3.25,3.7)	-0.64(-5.16,4.1)	0.73(-2.9,4.5)	-0.76(-3.79,2.36)
16	0.06(-3.94,4.23)	0.63(-3.43,4.87)	-0.66(-6.01,5)	1.26(-3.06,5.77)	-0.98(-4.5,2.68)

Note: Values were percentage increase (%) and 95% CI in risk of outpatient visits for TB.
The bold means statistically significant ($P < 0.05$).

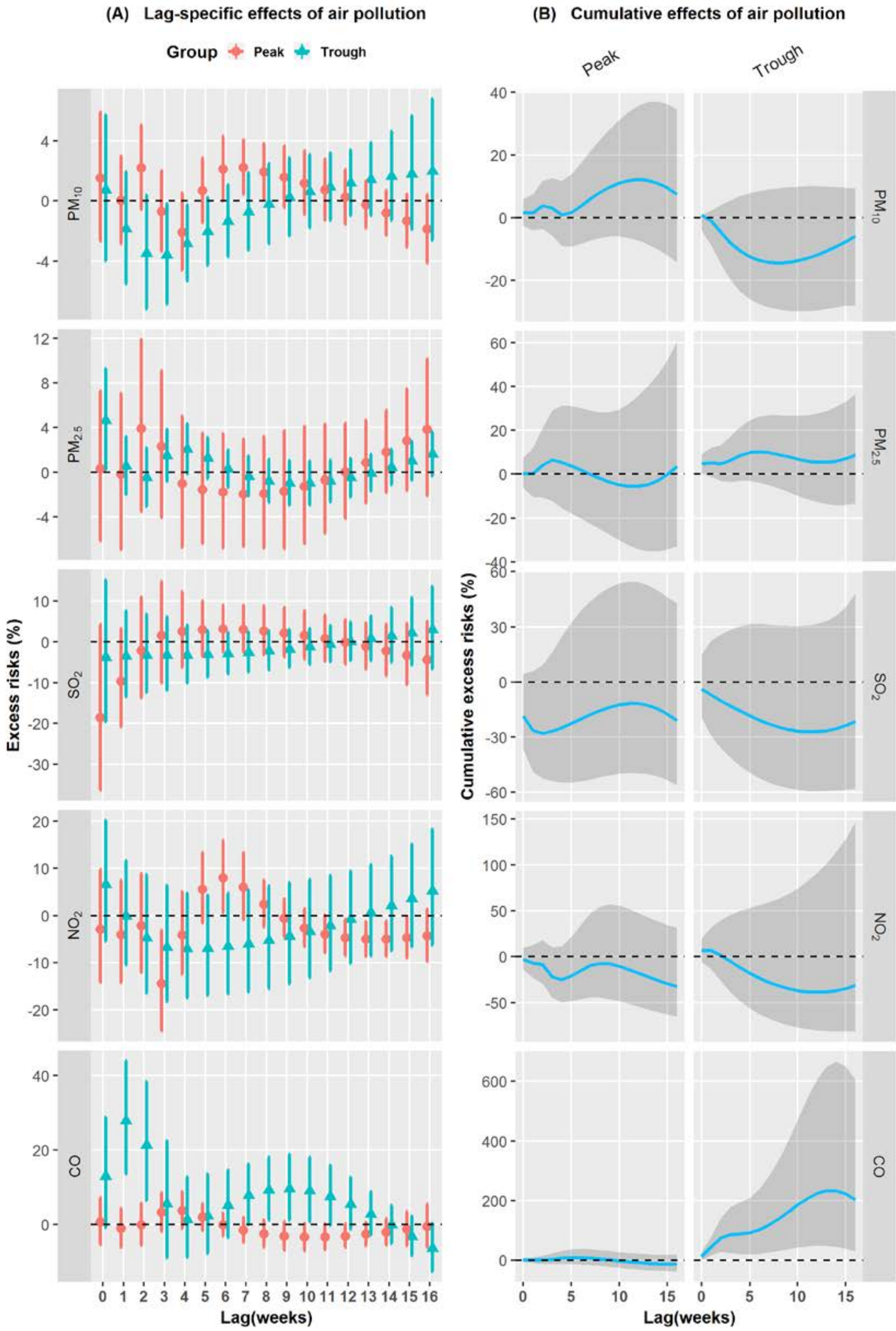
eTable 7

Lag-specific percentage changes (excess risk with 95% confidence interval) in initial outpatient visits for TB per 10 μg/m^3 increase in weekly mean concentrations of CO over lagged 16 weeks in single-pollutant models.

Lag (week)	All	15-59 years old	≥ 60 years old	Male	Female
0	-0.8(-3.07,1.53)	-1.19(-3.48,1.16)	3.46(-2.82,10.14)	-1.09(-3.32,1.19)	-0.2(-3.07,2.75)
1	0.57(-0.94,2.1)	0.47(-1.06,2.01)	-0.51(-4.7,3.85)	0.36(-1.04,1.79)	0.9(-1,2.85)
2	1.27(-0.36,2.93)	1.15(-0.5,2.82)	-0.36(-4.61,4.08)	1.29(-0.18,2.78)	1.34(-0.71,3.44)
3	1.1(-0.24,2.47)	0.67(-0.69,2.06)	**3.75(0.4,7.21)**	1.31(-0.12,2.75)	0.99(-0.7,2.7)
4	0.71(-0.71,2.16)	0.22(-1.22,1.67)	**5.2(1.47,9.08)**	0.84(-0.33,2.02)	0.58(-1.21,2.39)
5	0.32(-0.86,1.51)	-0.03(-1.22,1.17)	**4.08(0.91,7.35)**	0.39(-0.66,1.46)	0.26(-1.23,1.77)
6	0(-1.03,1.04)	-0.18(-1.22,0.87)	2.63(-0.21,5.55)	0.07(-1,1.15)	0(-1.3,1.33)
7	-0.23(-1.28,0.83)	-0.28(-1.34,0.79)	1.59(-1.37,4.64)	-0.15(-1.26,0.97)	-0.21(-1.54,1.13)
8	-0.38(-1.49,0.73)	-0.34(-1.45,0.79)	0.94(-2.24,4.22)	-0.28(-1.41,0.87)	-0.4(-1.79,1.02)
9	-0.47(-1.59,0.67)	-0.35(-1.48,0.8)	0.62(-2.7,4.06)	-0.32(-1.44,0.82)	-0.55(-1.97,0.9)
10	-0.49(-1.59,0.64)	-0.33(-1.44,0.8)	0.59(-2.78,4.08)	-0.28(-1.37,0.82)	-0.67(-2.07,0.74)
11	-0.45(-1.51,0.61)	-0.27(-1.33,0.8)	0.8(-2.55,4.27)	-0.19(-1.23,0.86)	-0.78(-2.11,0.57)
12	-0.37(-1.37,0.63)	-0.2(-1.2,0.81)	1.22(-2.09,4.65)	-0.04(-1.04,0.97)	-0.86(-2.11,0.41)
13	-0.26(-1.24,0.73)	-0.1(-1.08,0.89)	1.81(-1.54,5.28)	0.15(-0.86,1.18)	-0.93(-2.15,0.31)
14	-0.12(-1.16,0.93)	0.02(-1.03,1.07)	2.53(-1.01,6.19)	0.37(-0.73,1.49)	-0.98(-2.28,0.33)
15	0.04(-1.16,1.26)	0.14(-1.07,1.36)	3.34(-0.58,7.41)	0.62(-0.65,1.9)	-1.03(-2.52,0.48)
16	0.21(-1.23,1.67)	0.27(-1.18,1.74)	4.19(-0.28,8.87)	0.88(-0.61,2.39)	-1.08(-2.85,0.72)

Note: Values were percentage increase (%) and 95% CI in risk of outpatient visits for TB.
The bold means statistically significant ($P < 0.05$).

Section 4. Analysis stratified by season



eFigure 4. Lag-specific excess risks(%) (A) and cumulative excess risks(%) (B) in initial outpatient visits for TB per 10 units increase in weekly mean concentrations of air pollution over lagged 16 weeks in single-pollutant models stratified by the season of TB incidence.

eTable 8

Lag-specific percentage changes (excess risk with 95% confidence interval) in initial outpatient visits for TB per 10 units increase in weekly mean concentrations of air pollutants over lagged 16 weeks in single-pollutant models from March to August.

Lag (week)	PM_{10}	$PM_{2.5}$	SO_2	NO_2	CO
0	1.52(-2.69,5.91)	0.34(-6.14,7.27)	-18.58(-36.42,4.26)	-2.94(-14.18,9.78)	0.71(-5.42,7.24)
1	0.03(-2.84,2.98)	-0.17(-6.93,7.07)	-9.6(-20.9,3.31)	-4.02(-14.24,7.42)	-1.04(-6.1,4.29)
2	2.2(-0.55,5.03)	3.92(-3.48,11.88)	-2.13(-13.72,11.01)	-2.15(-12.03,8.83)	-0.07(-5.54,5.72)
3	-0.72(-3.37,2.01)	2.31(-4.05,9.09)	1.56(-10.13,14.77)	-14.44(-24.43,-3.13)	3.26(-1.77,8.54)
4	-2.09(-4.63,0.52)	-1.02(-6.73,5.03)	2.63(-6.25,12.35)	-4.1(-12.45,5.05)	3.78(-1.01,8.81)
5	0.67(-1.45,2.84)	-1.55(-6.38,3.52)	3.02(-3.54,10.03)	5.61(-1.64,13.4)	1.97(-1.56,5.63)
6	**2.12(0,4.29)**	-1.78(-6.77,3.48)	3.15(-2.45,9.07)	**8(0.63,15.9)**	-0.02(-3.01,3.06)
7	**2.22(0.43,4.05)**	-1.95(-6.63,2.98)	3.04(-2.53,8.94)	5.97(-0.9,13.32)	-1.49(-4.75,1.88)
8	**1.93(0.1,3.81)**	-1.93(-6.77,3.18)	2.73(-3.06,8.86)	2.39(-2.43,7.44)	-2.49(-6.09,1.24)
9	1.58(-0.45,3.65)	-1.69(-6.8,3.69)	2.22(-3.65,8.46)	-0.57(-4.5,3.52)	-3.1(-6.83,0.77)
10	1.17(-0.92,3.32)	-1.27(-6.36,4.09)	1.56(-4.19,7.66)	-2.63(-6.53,1.42)	-3.36(-6.99,0.4)
11	0.73(-1.28,2.77)	-0.68(-5.42,4.29)	0.76(-4.75,6.59)	-3.97(-7.89,0.11)	-3.34(-6.71,0.16)
12	0.24(-1.55,2.07)	0.04(-4.12,4.39)	-0.14(-5.49,5.51)	-4.72(-8.51,-0.78)	-3.06(-6.18,0.16)
13	-0.27(-1.83,1.32)	0.88(-2.75,4.65)	-1.13(-6.65,4.72)	-5.02(-8.64,-1.25)	-2.59(-5.7,0.62)
14	-0.8(-2.3,0.72)	1.81(-1.81,5.57)	-2.18(-8.34,4.4)	-4.98(-8.7,-1.1)	-1.98(-5.53,1.71)
15	-1.35(-3.09,0.43)	2.81(-1.65,7.47)	-3.25(-10.49,4.57)	-4.71(-9.04,-0.17)	-1.25(-5.69,3.39)
16	-1.89(-4.14,0.4)	3.84(-2.09,10.13)	-4.34(-12.93,5.09)	-4.32(-9.73,1.41)	-0.48(-6.09,5.47)

Note: Values were percentage increase (%) and 95% CI in risk of outpatient visits for TB.
The bold means statistically significant ($P < 0.05$).

eTable 9

Lag-specific percentage changes (excess risk with 95% confidence interval) in initial outpatient visits for TB per 10 units increase in weekly mean concentrations of air pollutants over lagged 16 weeks in single-pollutant models from September to February in next year.

Lag (week)	PM_{10}	$PM_{2.5}$	SO_2	NO_2	CO
0	0.74(-4,5.71)	**4.64(0.22,9.26)**	-3.73(-19.56,15.21)	6.6(-5.43,20.15)	13.02(-0.87,28.86)
1	-1.86(-5.52,1.94)	0.56(-2.01,3.2)	-3.47(-13.46,7.68)	-0.04(-10.48,11.61)	**27.89(13.65,43.91)**
2	-3.49(-7.22,0.39)	-0.47(-3.05,2.18)	-3.28(-12.43,6.82)	-4.74(-16.48,8.65)	**21.4(6.49,38.39)**
3	**-3.6(-6.86,-0.22)**	1.49(-0.79,3.82)	-3.23(-11.83,6.21)	-6.71(-18.19,6.37)	5.66(-8.81,22.42)
4	**-2.85(-5.34,-0.3)**	2.08(-0.14,4.35)	-3.21(-10.02,4.12)	-7.04(-17.47,4.72)	1.42(-8.79,12.78)
5	-2.05(-4.27,0.22)	1.27(-0.54,3.12)	-3.1(-8.62,2.76)	-6.9(-16.9,4.31)	2.33(-7.73,13.49)
6	-1.35(-3.7,1.06)	0.31(-1.34,1.99)	-2.89(-7.84,2.33)	-6.54(-16.57,4.69)	5.23(-3.4,14.63)
7	-0.74(-3.28,1.87)	-0.36(-2.11,1.43)	-2.58(-7.35,2.43)	-5.99(-16.16,5.41)	**7.87(0.07,16.28)**
8	-0.22(-2.84,2.48)	-0.78(-2.67,1.15)	-2.19(-6.86,2.72)	-5.25(-15.48,6.22)	**9.33(1.25,18.05)**
9	0.23(-2.34,2.86)	-0.97(-2.93,1.03)	-1.72(-6.26,3.05)	-4.35(-14.49,6.99)	**9.68(1.26,18.8)**
10	0.6(-1.81,3.07)	-0.97(-2.92,1.02)	-1.17(-5.56,3.41)	-3.3(-13.2,7.74)	**9.04(0.71,18.06)**
11	0.92(-1.31,3.2)	-0.79(-2.66,1.1)	-0.57(-4.91,3.96)	-2.11(-11.69,8.52)	7.58(-0.15,15.89)
12	1.19(-0.98,3.41)	-0.48(-2.22,1.28)	0.08(-4.53,4.9)	-0.8(-10.1,9.47)	5.45(-1.27,12.63)
13	1.42(-0.98,3.88)	-0.06(-1.68,1.59)	0.77(-4.55,6.39)	0.61(-8.62,10.77)	2.84(-2.8,8.81)
14	1.62(-1.31,4.64)	0.45(-1.14,2.07)	1.5(-4.97,8.42)	2.1(-7.43,12.61)	-0.09(-5.05,5.12)
15	1.8(-1.9,5.64)	1.02(-0.68,2.75)	2.26(-5.69,10.87)	3.66(-6.65,15.11)	-3.19(-8.36,2.27)
16	1.97(-2.62,6.78)	1.63(-0.33,3.62)	3.03(-6.58,13.63)	5.27(-6.3,18.26)	-6.31(-12.53,0.35)

Note: Values were percentage increase (%) and 95% CI in risk of outpatient visits for TB.

The bold means statistically significant ($P < 0.05$).

Section 5. Analysis at daily level

(1) Distributed lag nonlinear model (DLNM) at daily level

Here we developed a DLNM to assess non-linear exposure-response dependencies and lag effects of air pollution on TB cases at daily level. Suppose that Y_t , denotes the number of daily TB cases of the whole city, and follows a Poisson distribution by $Y_t|\mu_t \sim POI(\mu_t)$, where μ_t is the expected value of Y_t. Hence, we used a generalized additive regression with a log-linear Poisson model that allowed for overdispersion to combine a DLNM. The single-pollutant model specifications used for estimating the relationship between air pollution and initial TB cases at various single-day lags were as follows:

$$\log(\mu_t)=\alpha + \beta AP_{t,l} + ns(temp,3) + ns(humidity,3) + ns(wind,3) + ns(sunshine,3)$$
$$+ ns(time,7*4) + \lambda DOW + \delta Spring\text{-}festival$$
$$=\alpha + \beta C_{t,l} + COVs$$

where α is the intercept, and $AP_{t,l}$ is cross-basis matrix obtained by applying a DLNM to each indicator of air pollution.β is the coefficient for $AP_{t,l}$, l is the max lag days, and λ and δ stand for coefficients of the dummy variable for “day of week (DOW)” and the Spring Festival, which were used to exclude possible variations of initial TB outpatient visits within a week and during the Spring Festival. We used a natural cubic spline of time with 7 degrees of freedom (df) per year to control for the seasonality and the long-term trend of initial TB outpatient visits. We chose 7 degrees of freedom(df) based on model fit using Akaike’s information criterion (AIC) [1]. We fitted natural cubic splines with a priori 3 df to control for meteorological variables. In spearman correlation analysis, we noticed a strong negative correlation between temperature and air pressure (r = -0.91) and a strong positive correlation between relative humidity and rainfall (r = 0.69) (eTable 10). To avoid collinearity, air pressure and rainfall were excluded in the final models.

We separately developed the single-pollutant models over lagged 7, 14 and 21 days. To fully capture the overall impact of pollution and adjust for any potential harvesting, a maximum lag of 21 days was chosen for the pollution model based on the potential delayed periods of effects of air pollution on TB in a previous study[7] and exploratory analysis, as well as considering difficulty in interpretation with very long lags. Then we used a double natural cubic spline DLNM in which we fitted the natural cubic spline function to model both the nonlinear pollution effects and the lag effects. We set the medians of each pollutant concentration as reference values to calculate excess risks(%). We placed spline knots at equally spaced percentiles of pollution concentrations to allow sufficient flexibility at both ends of pollution concentration distribution; similarly, we laid spline knots at equally spaced $\log_{10}$-value scale of lags so that enough lag effects were allowed at shorter lag periods.[5] In order to build the best combination of the cross-basis function of air pollution and the lag in the two natural cubic splines, the optimal number of knots for each dimension was chosen on the basis of the smallest quasi-AIC (QAIC) .[1 6]

We estimated lag-specific excess risks (%) of air pollution on initial TB outpatient visits with an increase of 10 units in the concentrations of air pollution at various single-day lags (efigures 5-9). For instance, a lag of 0 day (unlagged) corresponds to the associations between air pollution in a given day and the risk of initial TB outpatient visits in that same day. Then we analyzed the relationship between air pollution and initial TB visits stratified by age and sex in the single pollutant model. Children (<15 years old) were excluded from subgroup analyses as the sample of this group was too small.

eTable 10

Spearman's correlation coefficients between daily air pollution and meteorological variables in Wuhan,2014-2017.

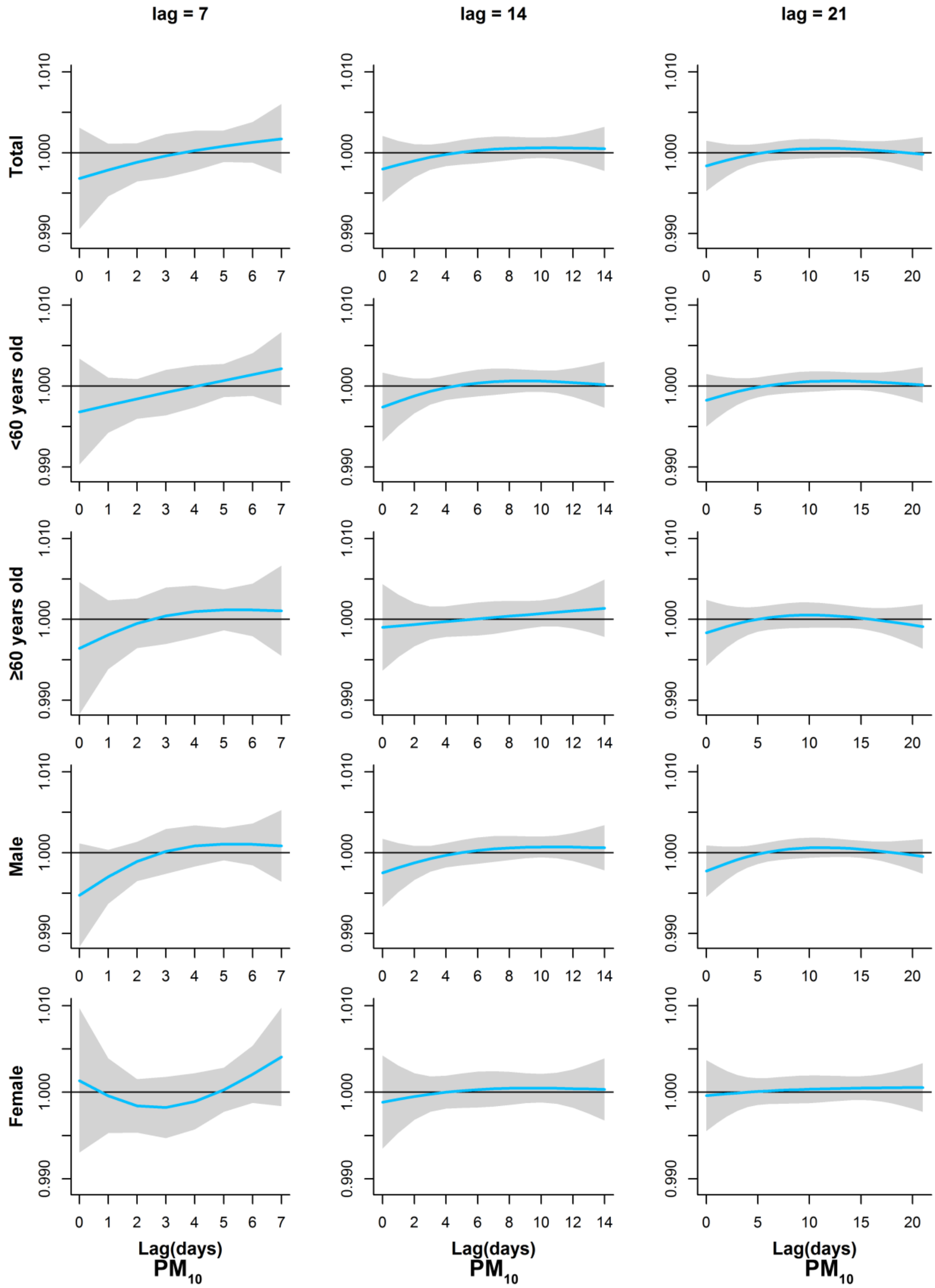
	$PM_{2.5}$	PM_{10}	SO_2	NO_2	CO	Temp	Humi	Press	Rain	Wind	Sun
$PM_{2.5}$	1	0.83 [a]	0.68 [a]	0.7 [a]	0.79 [a]	-0.52 [a]	-0.32 [a]	0.51 [a]	-0.33 [a]	-0.29 [a]	-0.02
PM_{10}		1	0.62 [a]	0.78 [a]	0.62 [a]	-0.26 [a]	-0.56 [a]	0.33 [a]	-0.51 [a]	-0.33 [a]	0.27 [a]
SO_2			1	0.6 [a]	0.54 [a]	-0.4 [a]	-0.48 [a]	0.44 [a]	-0.35 [a]	-0.26 [a]	0.11 [a]
NO_2				1	0.67 [a]	-0.38 [a]	-0.41 [a]	0.41 [a]	-0.43 [a]	-0.58 [a]	0.19 [a]
CO					1	-0.46 [a]	-0.05	0.4 [a]	-0.17 [a]	-0.31 [a]	-0.13 [a]
Temperature						1	0.13 [a]	-0.91 [a]	0.05	0.03	0.32 [a]
Humidity							1	-0.28 [a]	0.69 [a]	0.03	-0.59 [a]
Pressure								1	-0.22 [a]	-0.08 [b]	-0.15 [a]
Rainfall									1	0.28 [a]	-0.62 [a]
Wind										1	-0.15 [a]
Sunshine											1

PM_{10}: particulate matter < 10 μm in aerodynamic diameter; $PM_{2.5}$: particulate matter < 2.5 μm in aerodynamic diameter; SO_2: sulfur dioxide; NO_2: nitrogen dioxide; CO: carbonic oxide; O_3 : ozone.

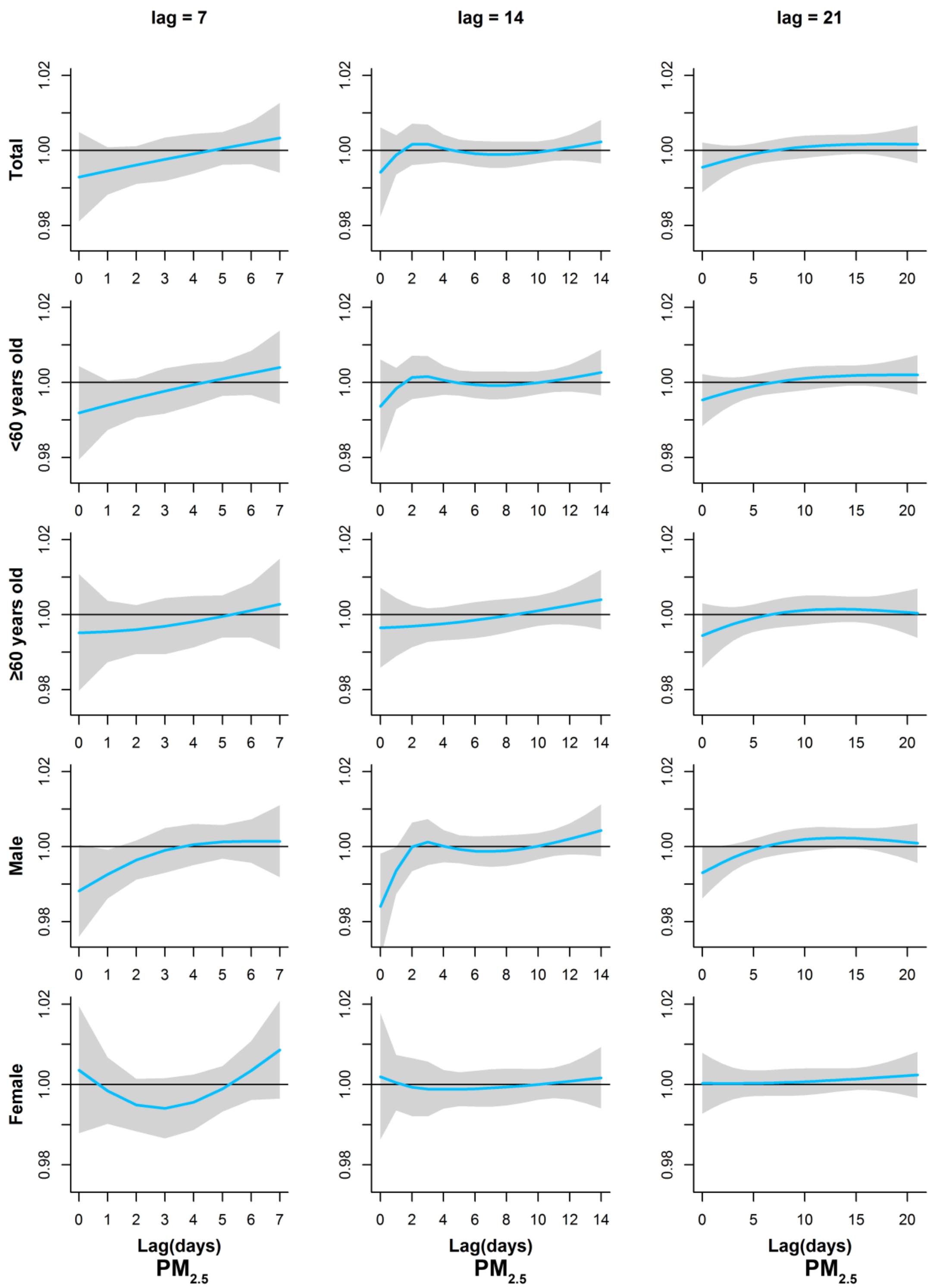
[a] $P < 0.001$.

[b] $P < 0.05$

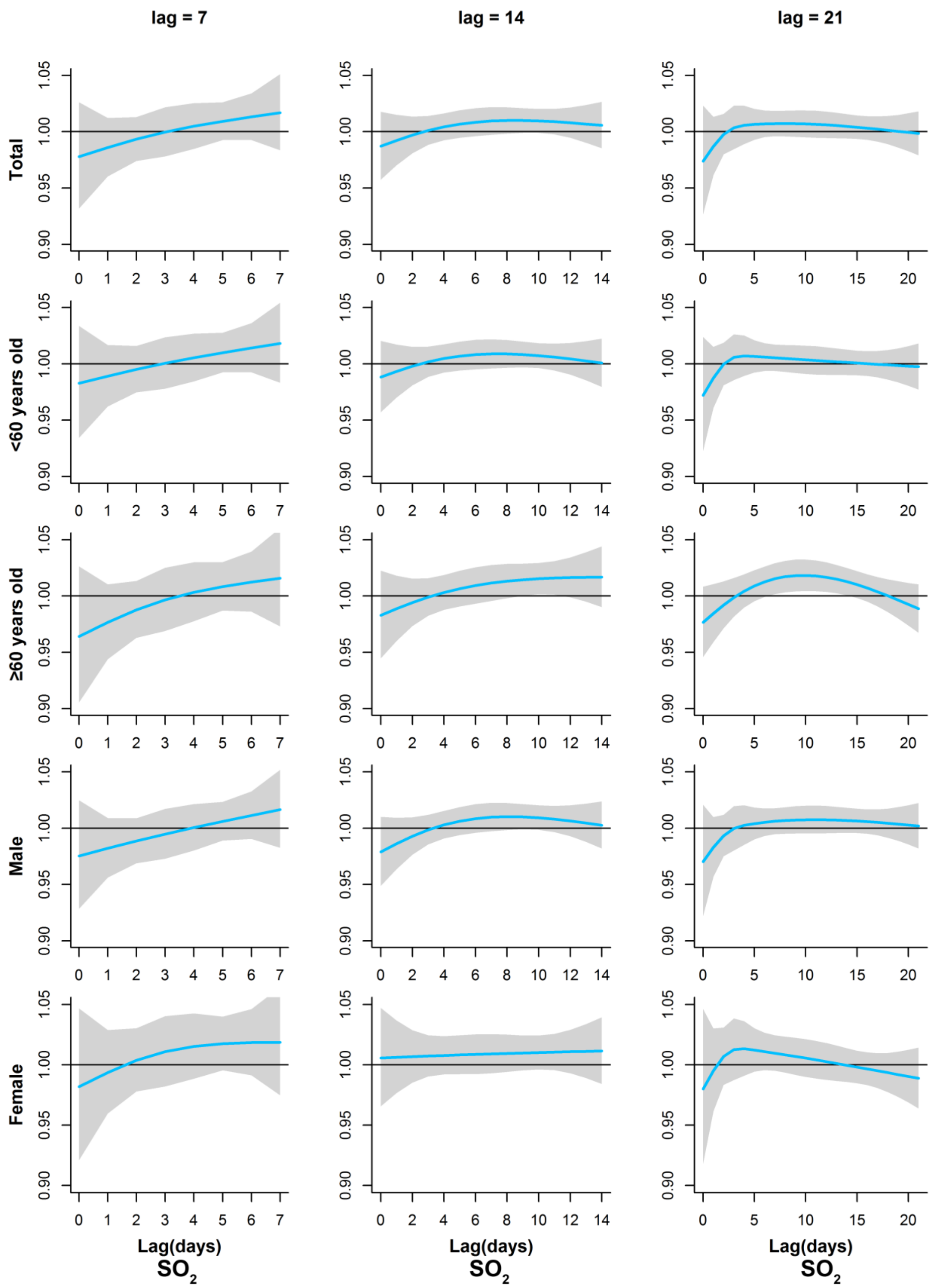
(2) Single-pollutant models in total population and subgroups at daily level



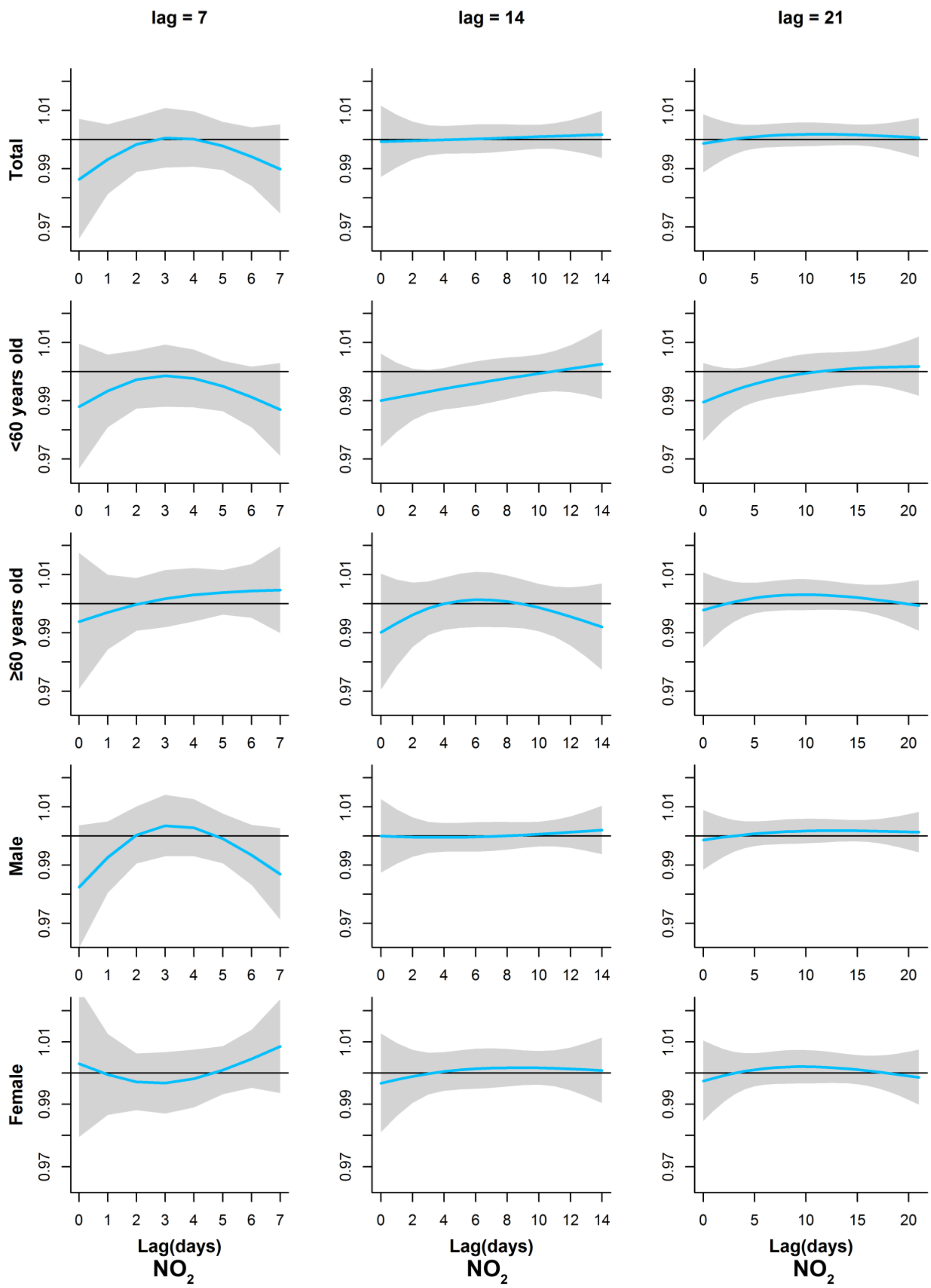
eFigure 5. Lag-specific relative risks in initial outpatient visits for TB per 10 μg/m^3 increase in weekly mean concentrations of PM_{10} over lagged 7, 14 and 21 days in single-pollutant models among all TB patients and subgroups stratified by age and sex.



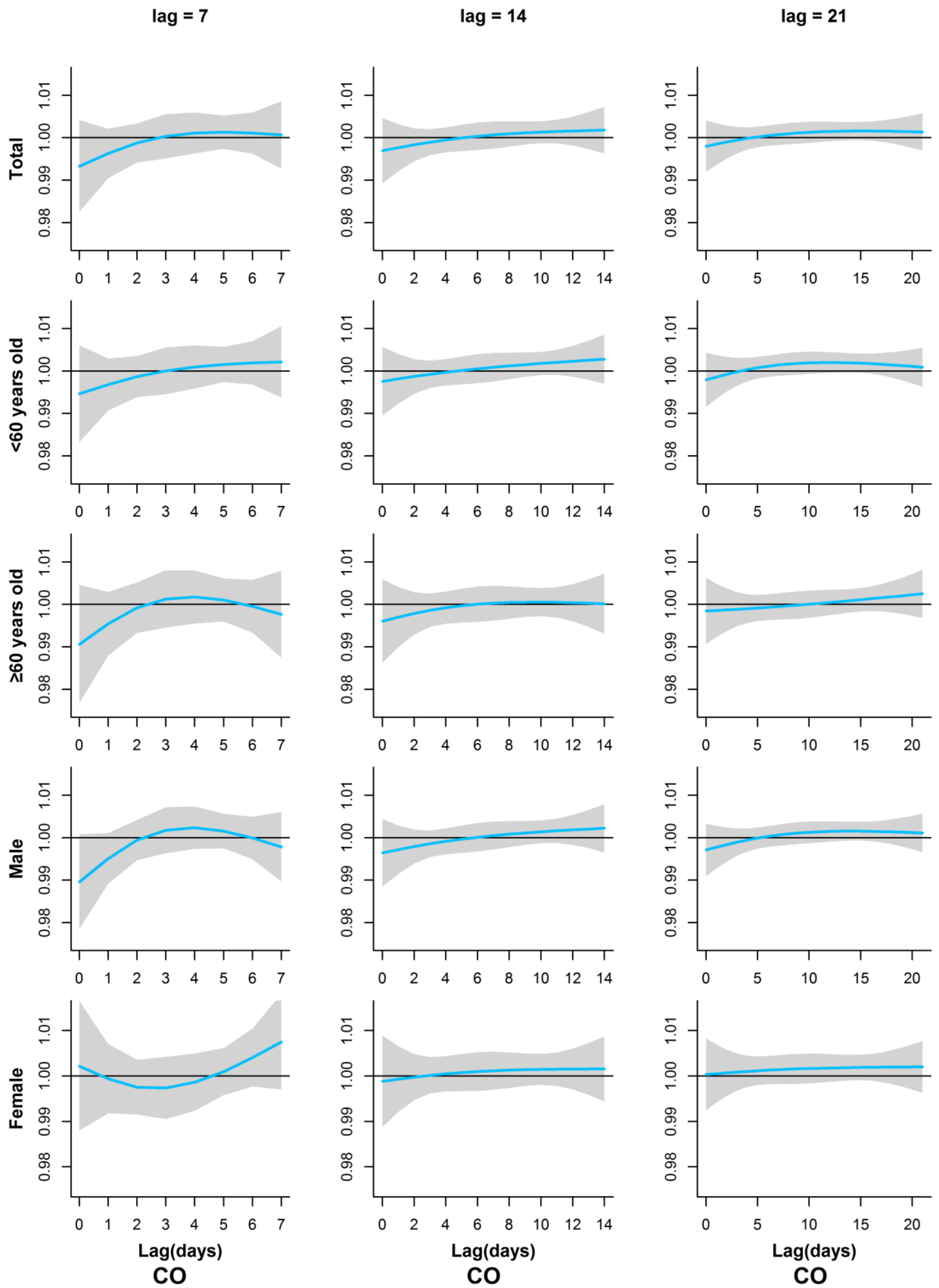
eFigure 6. Lag-specific relative risks in initial outpatient visits for TB per 10 μg/m^3 increase in weekly mean concentrations of $PM_{2.5}$ over lagged 7, 14 and 21 days in single-pollutant models among all TB patients and subgroups stratified by age and sex.



eFigure 7. Lag-specific relative risks in initial outpatient visits for TB per 10 μg/m^3 increase in weekly mean concentrations of SO_2 over lagged 7, 14 and 21 days in single-pollutant models among all TB patients and subgroups stratified by age and sex.



eFigure 8. Lag-specific relative risks in initial outpatient visits for TB per 10 μg/m^3 increase in weekly mean concentrations of NO_2 over lagged 7, 14 and 21 days in single-pollutant models among all TB patients and subgroups stratified by age and sex.



eFigure 9. Lag-specific relative risks in initial outpatient visits for TB per 0.1 mg/m3 increase in weekly mean concentrations of CO over lagged 7, 14 and 21 days in single-pollutant models among all TB patients and subgroups stratified by age and sex.

Section 6. Sensitivity Analysis

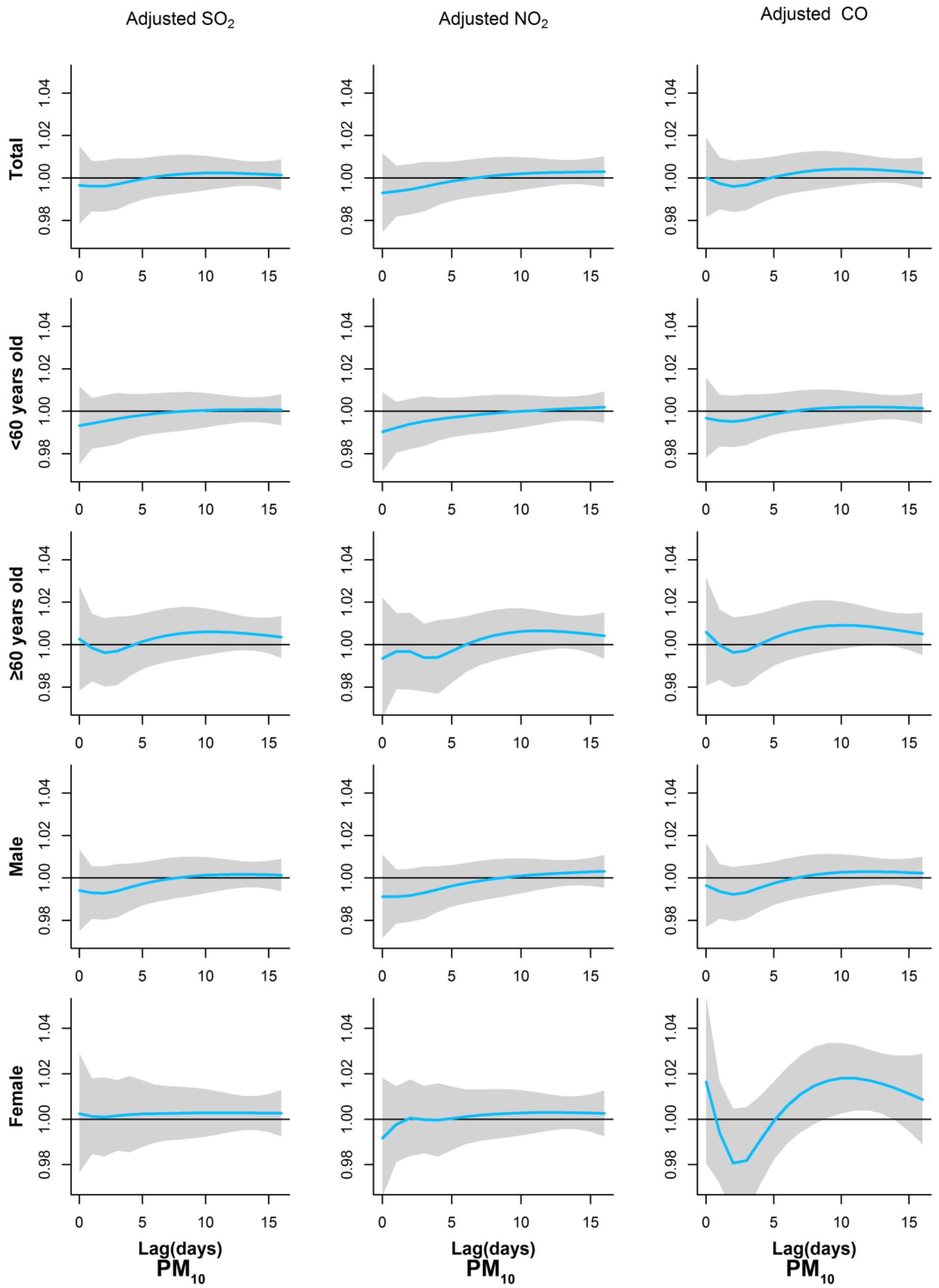
Based on the main models, we conducted several sensitivity analyses to assess the robustness of our results. Firstly, to eliminate the potential confounding factors caused by retreatment, we excluded 1,331(5.3%) retreated TB cases due to failure in the first treatment, recuperation of sputum smear-positive TB after full course of medication, irregular chemotherapy for more than one month or chronic persistent bacteriostasis. Secondly, two-pollutant models were applied to estimate percentage changes in lag-specific excess risks (%) of each air pollutant in the single-pollutant model among all TB cases and subgroups when stratified by age and sex. Thirdly, as the notified monthly TB case number was previously reported to be associated with the level of air pollution back to 3-6 months ago,[3] we changed the maximum lags from 16 weeks to 12 and 24 weeks in the final model. We then changed the df in the natural cubic spline of time from 6 df to 7 df per year to evaluate whether more flexible spline would have a substantial influence on our findings. Similarly, we changed the df in the natural cubic spline of meteorological factors from 3 df to 4 df.

We conducted a series of two-pollutant models (eFigure 10-14). When adjusted with CO, significant lag effects of PM_{10} at lag 9-13 weeks appeared among female patients, which indicated that CO might have potential synergistic effects on PM_{10}. When adjusted with NO_2, the observed lag effects of $PM_{2.5}$ at lag 1-2 weeks in the single-pollutant models among old patients extend to lag 2-5 weeks; when adjusted with CO, significant stronger lag effects of $PM_{2.5}$ were observed at lag 2-16 weeks among old patients. The findings indicated that CO and NO_2 might have potential synergistic effects on $PM_{2.5}$. When adjusted with PM_{10} or $PM_{2.5}$, the lag effect of SO_2

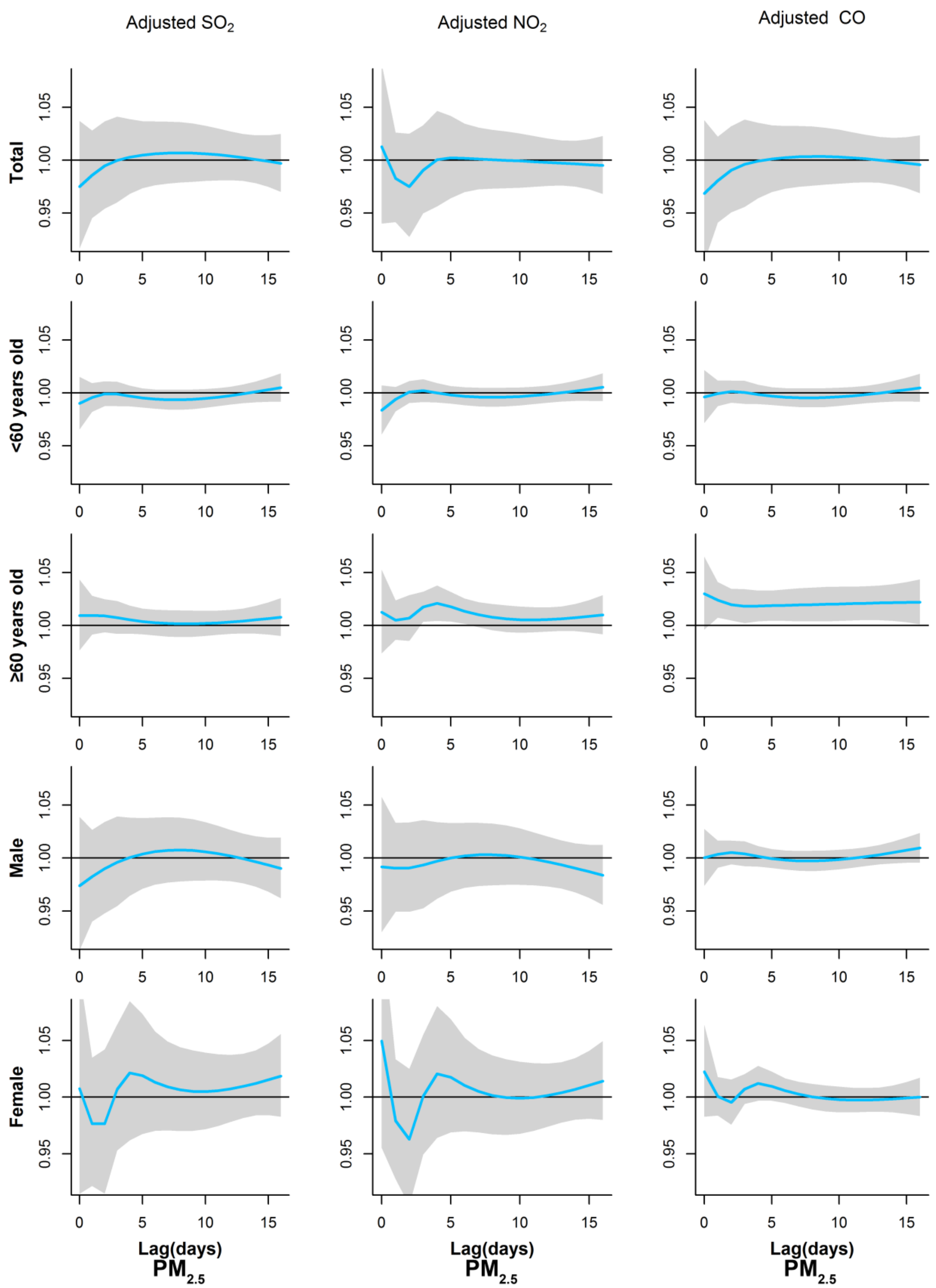
at lag 0 week among old patients was observed in the two–pollutant models but the positive effects at lag 0 among old patients in the single-pollutant model disappeared; When adjusted with NO_2, the lag effects of SO_2 at lag 0 week among the total patients and old patients and the additional positive effects at lag 11-13 weeks among old patients were observed in the two–pollutant models; When adjusted with CO, the lag effects of SO_2 at lag 5-6 weeks among the total patients and the additional effect at lag 3 week among the female patients were observed in the two–pollutant models, and other significant lag effects of SO_2 became stronger in two–pollutant models. When adjusted with PM_{10}, the observed lag effects of NO_2 at lag 0 week in the single-pollutant model among all TB patients, old patients and male ones became stronger but the lag effects of NO_2 at lag 2 week in the single-pollutant models among old patients was not significant; when adjusted with $PM_{2.5}$, the observed effects of NO_2 in the single-pollutant models were only significant among the male patients but not among all TB patients or old patients; when adjusted with SO_2, the observed effects of NO_2 at lag 0-1 weeks in the single-pollutant models were only significant among the old patients were only significant at lag 0 week ;when adjusted with CO, significant lag effects of NO_2 were observed at lag 0-1 weeks, lag 0 week and lag 0-1 weeks among all TB patients, old patients and male ones, respectively. The results indicated that PM_{10} and CO might have potential synergistic effects on NO_2 but $PM_{2.5}$ might have potential antagonistic effects on NO_2. When adjusted with $PM_{10,}$ the lag effects of CO were observed at lag week 4 and lag week 16; when adjusted with $PM_{2.5}$, the lag effects of CO were observed at lag 4-5 weeks; when adjusted with NO_2, the lag effects of CO were observed at lag 4-5 weeks and lag 15-16 weeks; when adjusted with SO_2, the lag effects of CO were only observed at lag 3. The results indicated that NO_2 might have potential synergistic effects on CO and SO_2 might have potential antagonistic effects on CO. Overall, the two-pollutant models indicated potential interactions between some pollutants.

Then, when we excluded retreated TB cases, the main results among all TB patients and subgroups were not greatly changed(eFigure 15-17). Finally, we changed the max lag period and the dfs of time and meteorological factors in the spline functions in the DLNM. When changing the max lags, patterns of associations between air pollutants and initial TB consults were generally similar to our main findings except the models of $PM_{2.5}$ (eFigure 18); when changing from 6 df to 7 df in the spline on the smoother time and changing from 3 df to 4 df in the spline on meteorological factors, the findings were generally similar to our main results (eFigure 19-20).

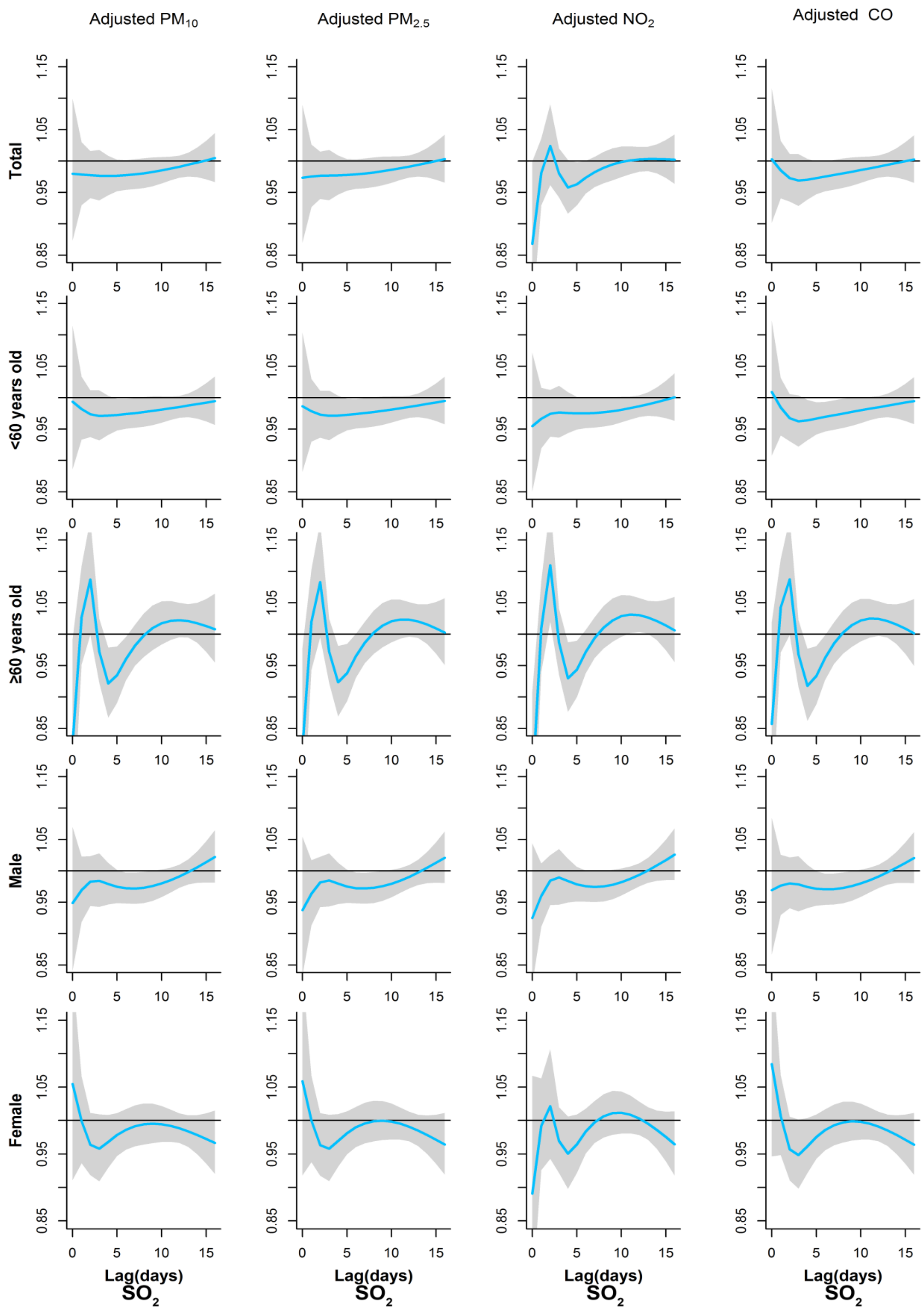
(1) Sensitivity analysis fitting two-pollutant models



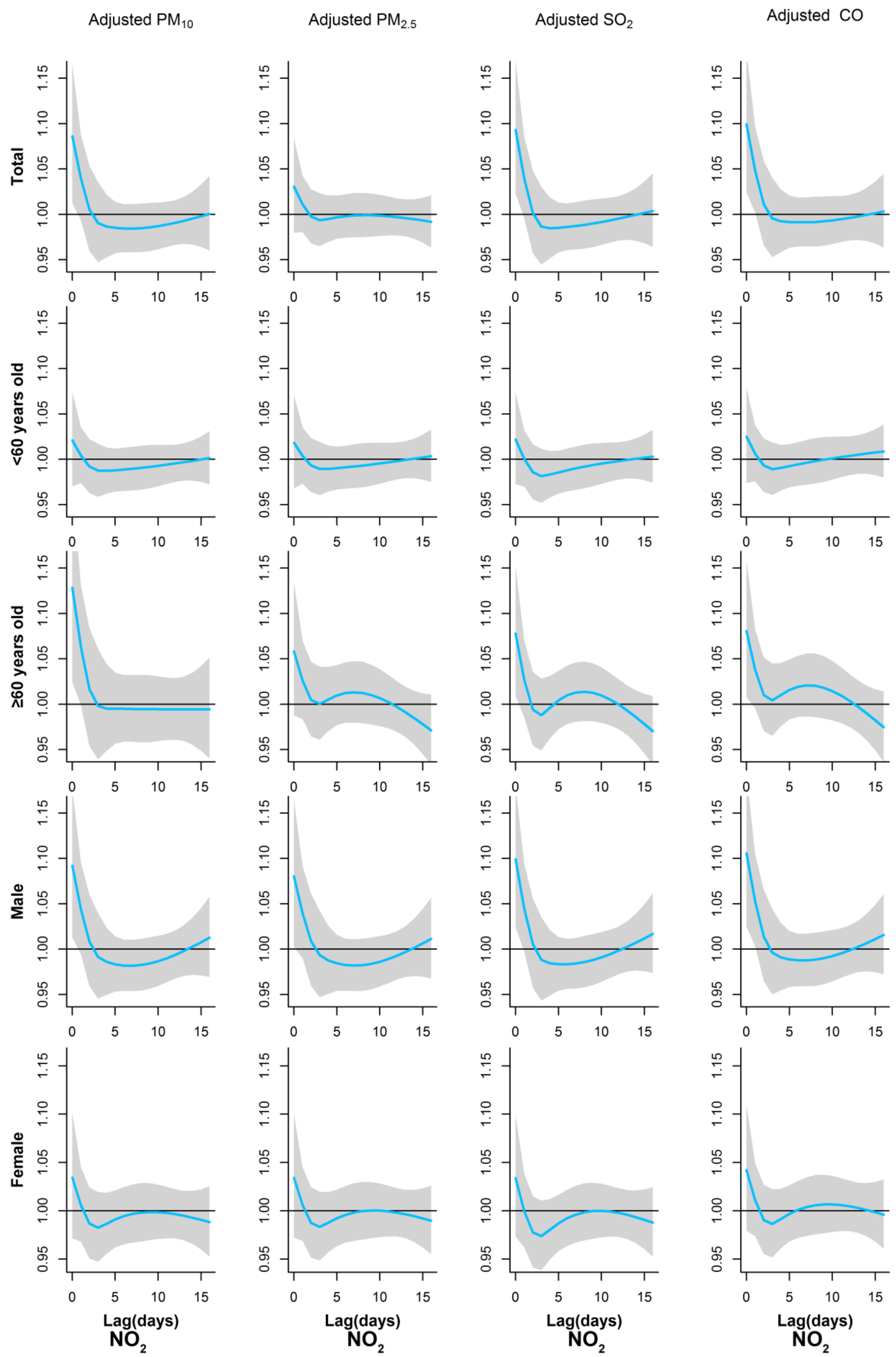
eFigure 10. Lag-specific relative risks (95% confidence interval) in initial outpatient visits for TB per 10 μg/m3 increase in weekly mean concentrations of PM_{10} adjusted with SO_2, NO_2 or CO over lagged 16 weeks in two-pollutant models.



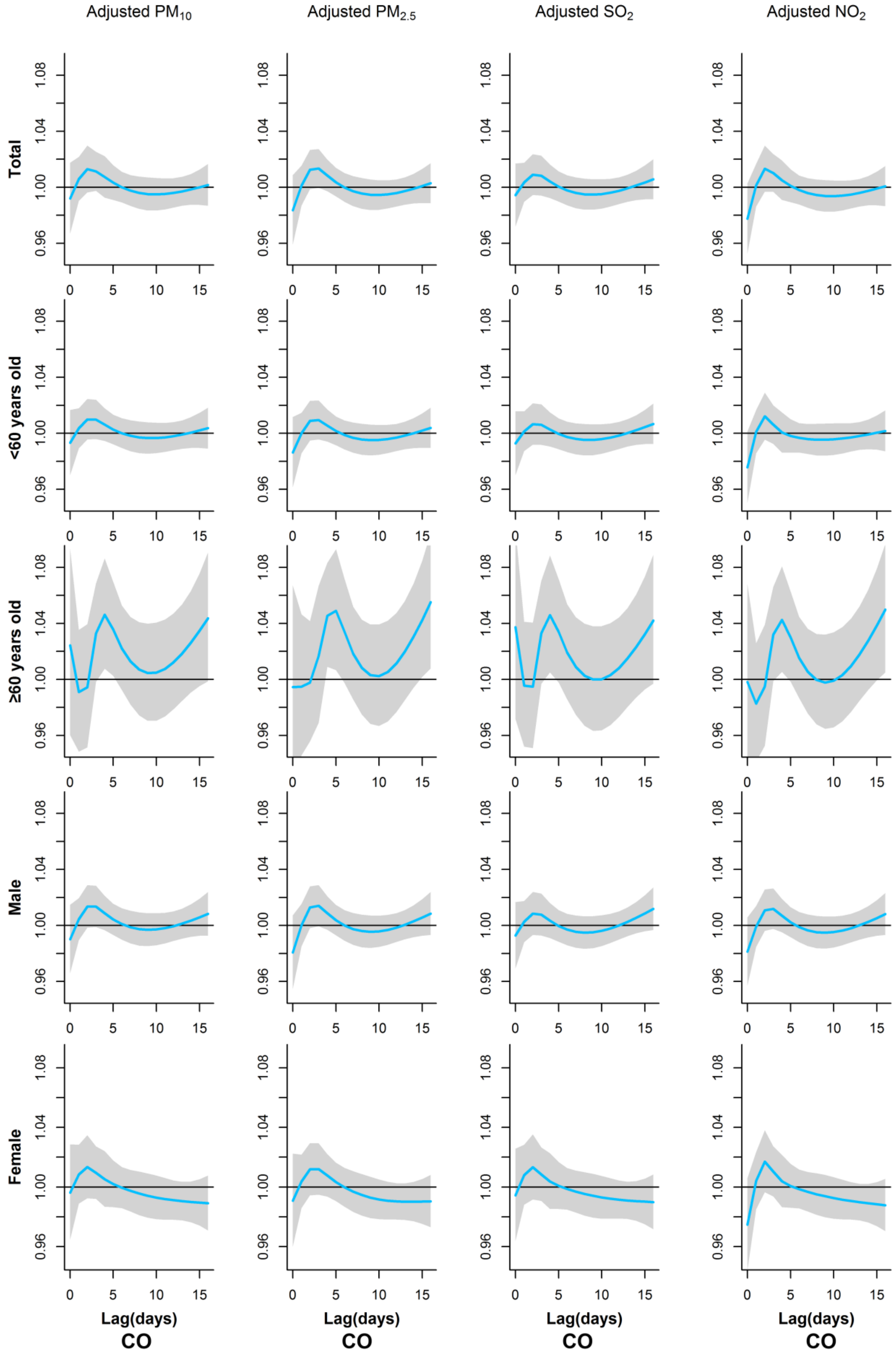
eFigure 11. Lag-specific relative risks (95% confidence interval) in initial outpatient visits for TB per 10 μg/m3 increase in weekly mean concentrations of $PM_{2.5}$ adjusted with SO_2, NO_2 or CO over lagged 16 weeks in two-pollutant models.



eFigure 12. Lag-specific relative risks (95% confidence interval) in initial outpatient visits for TB per 10 μg/m3 increase in weekly mean concentrations of SO_2 adjusted with PM_{10}, $PM_{2.5}$, NO_2 or CO over lagged 16 weeks in two-pollutant models.

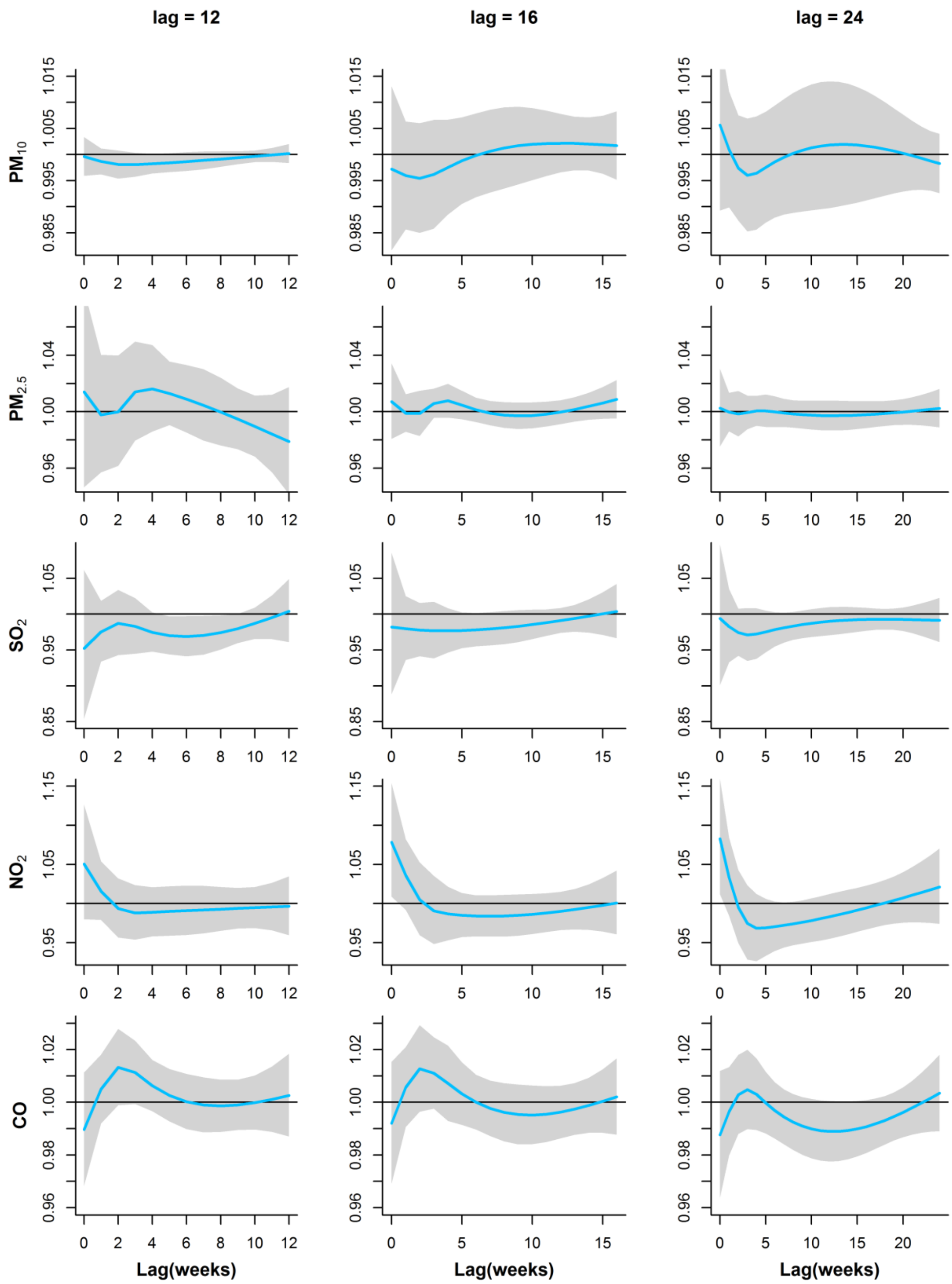


eFigure 13. Lag-specific relative risks (95% confidence interval) in initial outpatient visits for TB per 10 μg/m3 increase in weekly mean concentrations of NO_2 adjusted with PM_{10}, $PM_{2.5}$, SO_2 or CO over lagged 16 weeks in two-pollutant models.

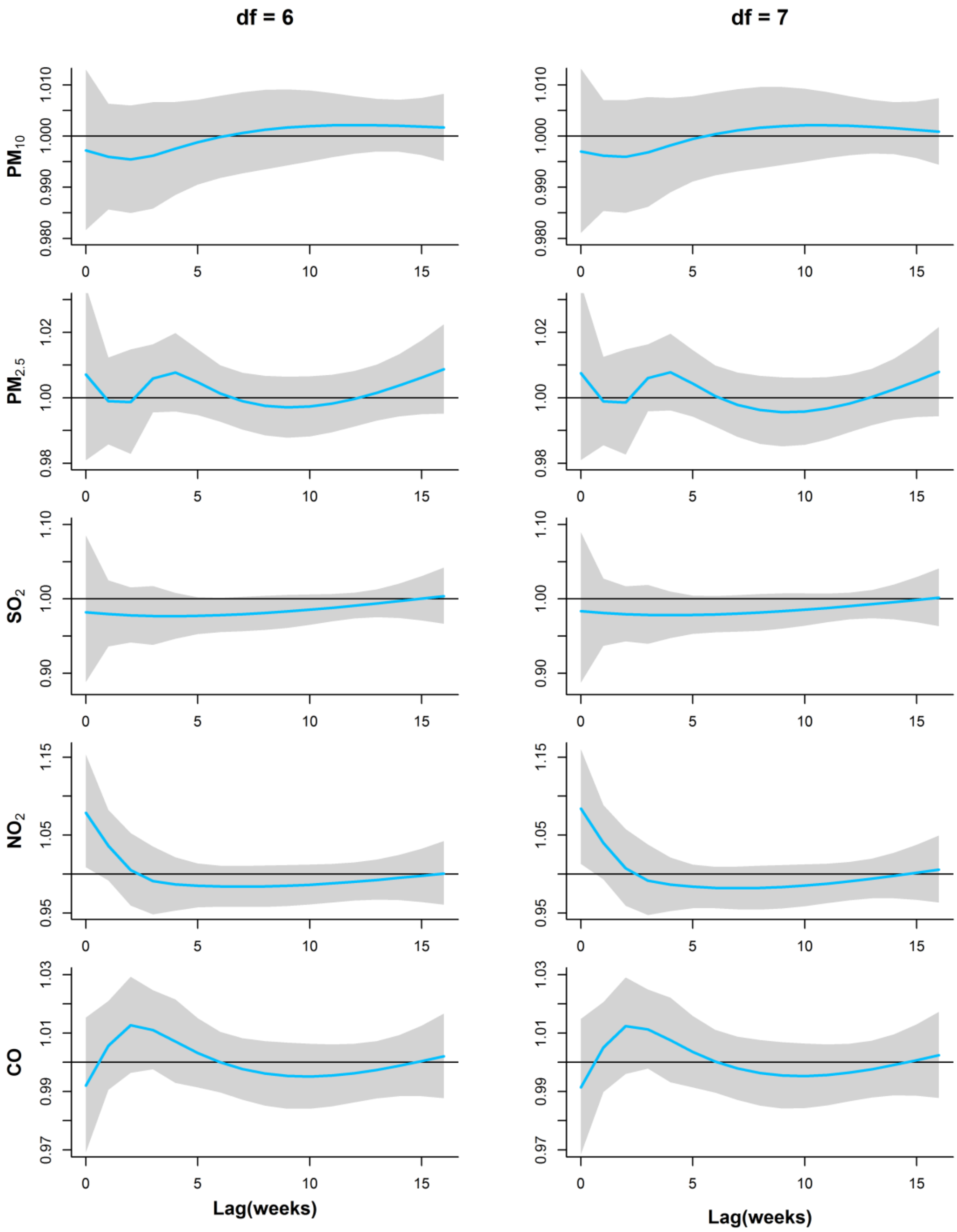


eFigure 14. Lag-specific relative risks (95% confidence interval) in initial outpatient visits for TB per 10 μg/m3 increase in weekly mean concentrations of CO adjusted with PM_{10}, $PM_{2.5}$, SO_2 or NO_2 over lagged 16 weeks in two-pollutant models.

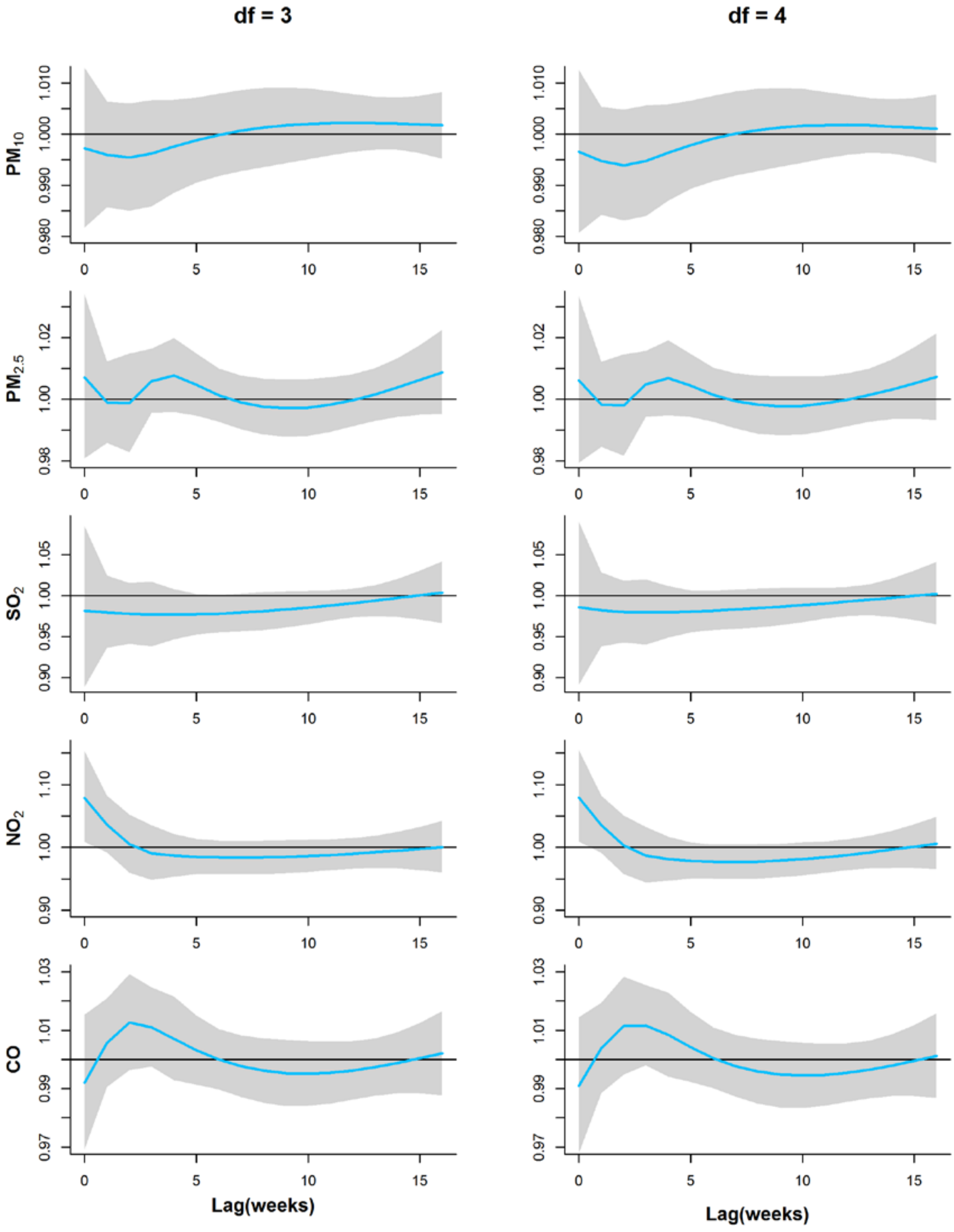
(3) Sensitivity analysis changing maximum lag and df in DLNM



eFigure 18. Lag-specific relative risk in initial outpatient visits for TB per 10 units increase in weekly mean concentrations of air pollution over the maximum lags of 12 weeks, 16 weeks and 24 weeks in single-pollutant models.



eFigure 19. Lag-specific relative risk in initial outpatient visits for TB per 10 units increase in weekly mean concentrations of air pollution over lagged 16 weeks in single-pollutant models with 6 df and 7 df in the natural cubic spline of time (weeks).



eFigure 20. Lag-specific relative risk in initial outpatient visits for TB per 10 units increase in weekly mean concentrations of air pollution over lagged 16 weeks in single-pollutant models with 3 df and 4 df in the natural cubic spline of meteorological factors.

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