Air Pollutant Sulfur Dioxide is a Major Risk Factor for Pulmonary Tuberculosis Hospitalizations of HIV-infected Patients: Distribution Lag Non-linear Analyses

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Abstract

Background: The relationship between air pollutants and pulmonary tuberculosis (PTB) in HIV-infected patients, an immunocompromised population, is unclear.

Methods: The data of PTB cases among HIV-infected patients admitted to Guangzhou Eighth People's Hospital, the local largest HIV/AIDS treatment clinic, as well as the meteorological factors and air pollutants between 2014 and 2019, were collected. The associations between air pollutants and PTB were evaluated in generalized linear model (GLM) and distributed lag non-linear model (DLNM). The robustness of results was tested by sensitivity analysis.

Results: A total of 494 subjects were enrolled. PTB cases were decreased over time and significantly correlated with monthly mean concentrations of sulfur dioxide (SO_2, r = 0.5, P < 0.001) but not other pollutants. In multi-pollutant GLM, SO_2 was a risk factor of monthly PTB cases (relative risk [RR] =1.160, 95% confidence interval [CI]: 1.105-1.218) and fine particulate ($PM_{2.5}$) was a protective factor (RR = 0.971, 95% CI: 0.950-0.993). In single-pollutant DLNM, a 10-unit increase in SO_2 concentration was significantly related to PTB cases within lag 0-6 months with the peak RR at lag 0 month (RR = 1.201, 95% CI: 1.028-1.403) and linearly decreased over lag months, and the cumulative effect reached the peak at lag 13 month (RR = 3.672, 95% CI = 1.052-12.81). In multi-pollutant DLNM, SO_2 remained a risk factor of PTB within lag 0-3 months. $PM_{2.5}$ was negatively associated with PTB at lag 18 month (RR = 0.900, 95% CI: 0.810-0.999) in single-pollutant DLNM and not significant in multi-pollutant DLNM.

Conclusions: SO_2 is identified as a major risk factor of PTB in HIV-infected patients.

Background

Tuberculosis is an airborne wasting infectious disease caused by Mycobacterium tuberculosis mainly invading lung tissue. In 2020, tuberculosis contributed to a total of 1.5 million death worldwide including ~ 2 million HIV (human immunodeficiency virus)-infected patients, representing the second leading infectious killer only after coronavirus disease 2019 (COVID-19) (1). Despite tremendous efforts to reduce the incidence and mortality, China remains one of the highest-tuberculosis burden countries in the world, accounting for 9% of global total cases in 2018 (1–3). Poor socio-economic status, weakened immune system (HIV infection, malnutrition, and diabetes), alcohol abuse, active smoking, and indoor pollution are associated with tuberculosis (4, 5), and among them, HIV infection, which significantly accelerates the deterioration of host immunological functions, is one of the most powerful known risk factors (6). Although about one-third of global population can expect Mycobacterium tuberculosis infection during lifetime, only approximately 10% of them eventually develop active tuberculosis, but in HIV-infected patients, this risk could be increased to 5%-10% annually (7, 8). Tuberculosis can occur in HIV-infected patients at any stage of CD4 cells depletion, and CD4 cell count is the dominant predictor for this contagious disease (9, 10). Besides, CD8 T cells, $FoxP3^+$ Treg cells, and granuloma formation are also

involved in tuberculosis activation among HIV-infected patients (11–15), but the detailed mechanism needs further research.

Recent studies showed that outdoor pollution may accelerate tuberculosis development (16). Air pollutants are thought to interfere with non-specific and specific lung defense functions, induce oxidative stress and inflammatory reaction, and reduce host immunity to exogenous substances (17, 18), which are likely to account for their adverse effect on tuberculosis pathogenesis. However, the conclusions concerning the impact of fine particulate ($PM_{2.5}$) on tuberculosis are not consistent in epidemiological studies (19, 20). Additionally, some groups reported that long term exposure to sulfur dioxide (SO_2) increased tuberculosis risk in males (19), while other studies suggested a protective role of low levels of SO_2 (21). On the other hand, the host immune status, e.g., HIV infection, the most potent predictor for tuberculosis, was not taken into account in the research, and there were limited studies focused on HIV-infected patients (22). There might be distinct hypotheses for tuberculosis development in this specific population: HIV infection exacerbates the adverse effect of certain air pollutants, and the latter play a significant role in tuberculosis events; alternatively, the impact of air pollution is undermined by extremely weakened host immune system, and the patients develop tuberculosis regardless of the variation of air pollutant concentrations. Unfortunately, by now comprehensive assessments of the relationship between air pollutants and tuberculosis among HIV-infected patients, especially in China, are lacking.

Guangzhou Eighth People's Hospital is the training base for clinicians in HIV and acquired immune deficiency syndrome (AIDS) in Guangzhou with more than 80% of local HIV-infected patients enrolled during the last decade (23). This study aims to explore the potential link between air pollutants and pulmonary tuberculosis (PTB) events among HIV-infected patients based on distribution lag non-linear analyses.

Methods

Study population

The study was approved by the Ethics Committee of Guangzhou Eighth People's Hospital. The hospitalization date, diagnosis, CD4 cell count, age, and sex were extracted from the records from January 1, 2014, through December 31, 2019. Informed consent was exempted because individual identifiers were not used. The diagnosis of PTB in HIV-infected patients was based on medical history, symptoms, physical examinations, and laboratory tests, e.g., isolation of mycobacterium tuberculosis from sputum or bronchoalveolar lavage, and confirmed by at least two physicians. The patients who resided outside Guangzhou city were excluded. In case of repeated hospitalizations, only the first admission was included.

Meteorological and air pollutants data

The daily data of meteorological factors including temperature, humidity, wind speed, and pressure, and air pollutants including $PM_{2.5}$, SO_2, carbon monoxide (CO), nitrogen dioxide (NO_2), and ozone (O_3) in

Guangzhou were collected from Weather Underground, IBM (https://www.wunderground.com) and National Air Quality Study Platform (https://www.aqistudy.cn), respectively, as described in our previous study (24). The monthly mean concentrations of these variables were calculated for further analyses.

Statistical analyses

Spearman's rank correlation and scatter plot were used to explore the relationships between PTB cases and incidence, meteorological factors, and air pollutants. In generalized linear model (GLM), we included meteorological factors, humidity, and wind speed, which correlated with PTB cases with a P value less than 0.4 in order to minimize the loss of information. Other meteorological factors, temperature and pressure, were excluded because they had little correlation with PTB cases ($P > 0.4$) but strongly correlated with various air pollutants ($|r| > 0.7$), indicating collinearities between them(17, 25). We adopted a quasiPoisson regression model to combine a GLM:

$Y_t \sim \text{quasiPoisson}(\mu_t)$

$\text{Log}(\mu_t) = \alpha + \beta_1\,(\text{air pollutant}) + \text{ns}(\text{humidity}, df_1) + \text{ns}(\text{wind speed}, df_2) + \beta_2\,(\text{month})$

Y_t represents the number of monthly PTB cases or incidence, and μ_t is the expected value of Y_t. The meteorological factors of humidity and wind speed were controlled by a natural cubic spline function (ns) with three degrees of freedom (df_1 and df_2) in accordance with previous reports (26, 27). The variable "month" was used to control the impact of months. Air pollutants with a P value less than 0.15 in single-pollutant model were entered into multi-pollutant analyses.

We also established distributed lag non-linear models (DLNM) (28) to explore the associations between air pollutants and PTB cases. The variables in DLNM were similar to those in GLM except that a cross-basis function for air pollutants, as well as a "time" variable for controlling long-term trends, were used. In cross-basis functions, "ns" and "poly" functions were applied to fit the exposure-response and lag-response relationship (28). Given that the incubation period of tuberculosis is typically no more than two years (median, 15.38 months) (29–31), the maximum lag was set to 18 months via exploratory analysis (31). To evaluate the effect of air pollutant exposure on PTB cases, the median concentration of each pollutant was set as a reference (32), and the relative risk (RR) and cumulative RR for a 10-unit increase in the concentration of each air pollutant were calculated. The DLNM model is as follows:

$Y_t \sim \text{quasiPoisson}(\mu_t)$

$\text{Log}(\mu_t) = \alpha + \beta_1 T_{t,l} + \text{ns}(\text{humidity}, df_1) + \text{ns}(\text{wind speed}, df_2) + \beta_2\,(\text{month}) + \beta_3\,(\text{time})$

$T_{t,l}$ represents the cross-basis function for air pollutants.

Sensitivity analyses were conducted to confirm the robustness of our results: (1) change the degrees of freedom (1, 2, and 4–8 df) in the "ns" function of humidity and wind speed variables in GLM; (2) change the maximum lag of 18 months to 12 or 6 months in DLNM. The analyses were performed with "dlnm"

packages in R software (version 4.1.1). All P values were two-sides and a P value less than 0.05 was considered statistically significant.

Results

Patients and environmental data

This study included 494 hospitalized HIV-infected patients diagnosed as PTB between 2014 and 2019 (Fig. 1 and Table 1). The majority were male (n = 419, 84.8%), and the median age was 43 years. The median CD4 cell count was 57 cells/μL at admission, and the most common co-infection and comorbidity were oral candida (n = 126, 25.6%) and heart disease (60, 12.1%), respectively. During the study period, the number of admitted HIV-infected patients gradually increased. In contrast, PTB cases among them significantly decreased from 111 in 2014 to 43 in 2019 ($P < 0.001$, Figure S1A, S1B, and Table S1). Given that HIV infection is a well-known risk factor of PTB, we also evaluated the PTB cases adjusted for HIV infection, and defined “PTB incidence” as the number of PTB cases per 1000 HIV admissions. We found that PTB incidence also significantly decreased over time ($P < 0.001$, Figure S1A, S1B, and Table S1). Besides, there was no obvious fluctuation of PTB cases and incidence among months (Figure S1C and S1D).

Table 1
Demographic and clinical features of HIV-infected patients with pulmonary tuberculosis (n = 494).

Demographic characteristic	Value
Male	419 (84.8%)
Age, years	43 (36–54)
Occupation	
Worker	109 (22.1%)
Farmer	14 (2.8%)
Staff	30 (6.1%)
Retired	28 (5.7%)
Student	6 (1.2%)
Other*	212 (42.9%)
Unemployed	95 (19.2%)
CD4 cell count, cells/μL	57 (22.5-167.5)
Co-infection	
Talaromycosis	33 (6.7%)
Cryptococcus neoformans infection	18 (3.6%)
Oral Candida	126 (25.5%)
Pneumocystis pneumonia	66 (13.4%)
Viral hepatitis	156 (31.6%)
Syphilis	88 (17.8%)
Comorbidity	
Diabetes	20 (4.0%)
Liver cirrhosis	14 (2.8%)
Hypertension	38 (7.7%)
Heart diseases	60 (12.1%)

Data are in absolute count (%) for categorical variables and median (interquartile range [IQR]) for continuous data. Other*, self-employed or unknown occupations.

The summary statistics of meteorological factors and air pollutants during the study period are reported in Table S2. The monthly mean concentrations of three air pollutants, $PM_{2.5}$, SO_2, and CO, were significantly decreased over the years, while the levels of NO_2 and O_3 remained stable (Figure S1B and Table S1). The monthly kinetics curves of various air pollutants were also distinct, e.g., contrary to other pollutants, the concentration of SO_2 remained stable every month, similar to those of PTB cases and incidence (Figure S1C and S1D). In correlation analyses (Figure S2 and S3), SO_2 was significantly correlated with PTB cases ($r = 0.5$, $P < 0.001$) and incidence ($r = 0.66$, $P < 0.001$), $PM_{2.5}$ was weakly correlated with incidence ($r = 0.21$, $P = 0.022$), and other pollutants were not significantly correlated with PTB cases or incidence.

Associations between PTB cases, incidence and air pollutants

We evaluated the potential link between air pollutants and PTB cases in GLM including meteorological factors humidity and wind speed in cubic spline functions, and "month" variable for controlling the month effect, and found $PM_{2.5}$ (RR = 1.022, 95% CI: 1.006–1.038), SO_2 (RR = 1.101, 95% CI: 1.067–1.137), and CO (RR = 6.813, 95% CI: 1.622–28.79) were significantly associated with PTB cases in single-pollutant model (Table 2). However, in multi-pollutant analyses, only SO_2 was a risk factor of PTB cases (RR = 1.160, 95% CI: 1.105–1.218), $PM_{2.5}$ turned negatively associated with PTB cases (RR = 0.971, 95% CI: 0.950–0.993), and CO was not significant (RR = 1.029, 95% CI: 0.210–5.013). Likewise, PTB incidence was significantly and positively associated with SO_2 (RR = 1.222, 95% CI: 1.159–1.290) but not other pollutants in the multi-pollutant model (Table S3).

Table 2
Associations between air pollutants and PTB cases in GLM.

Variable	Single-pollutant		Multi-pollutant	
	RR (95% CI)	P value	RR (95% CI)	P value
$PM_{2.5}$ (μg/m^3)	1.022 (1.006–1.038)	0.010	0.971 (0.950–0.993)	0.012
SO_2 (μg/m^3)	1.101 (1.067–1.137)	< 0.001	1.160 (1.105–1.218)	< 0.001
NO_2 (μg/m^3)	1.006 (0.985–1.027)	0.593	-	-
CO (mg/m^3)	6.813 (1.622–28.79)	0.012	1.029 (0.210–5.013)	0.972
O_3 (μg/m^3)	0.997 (0.986–1.009)	0.656	-	-

The variables with $P < 0.15$ in single-pollutant model were combined for multi-pollutant analyses. RR, relative risk; CI, confidence interval.

Since SO_2 and $PM_{2.5}$ respectively represented a risk factor and protective factor of PTB cases in multi-pollutant GLM, we further evaluated their relationships using DLNM, which have been recently applied for

studying environmental impact on health outcomes (17, 27, 31–34). In single-pollutant DLNM, a comprehensive summary of the association between SO_2 and PTB cases over an 18-month period is shown in Fig. 2A and 2B. In general, an increased risk of PTB was positively associated with elevated concentrations of SO_2 but negatively associated with lag months. A 10-unit increase in SO_2 concentration was significantly related to PTB cases within lag 0–6 months with the peak RR at lag 0 month (RR = 1.201, 95% CI: 1.028–1.403) and the minimum RR at lag 6 month (RR = 1.105, 95% CI: 1.007–1.213, Fig. 2C and Table 3). The cumulative RR of a 10-unit increase in SO_2 concentration continuously increased from lag 0 month and reached the peak at lag 13 month (RR = 3.672, 95% CI:1.052–12.81, Fig. 2D and Table 3). For $PM_{2.5}$, we did not find its significant association with PTB cases during most of the lag periods except a negative link at lag 18 month (RR = 0.900, 95% CI: 0.810–0.999, Figure S4 and Table 3). We also established SO_2-$PM_{2.5}$ multi-pollutant DLNM, and the results were similar, that a 10-unit increase in SO_2 concentration was significantly related to PTB cases within lag 0–3 months with the peak RR at lag 0 month (RR = 1.384, 95% CI: 1.012–1.893) and the minimum RR at lag 3 month (RR = 1.337, 95% CI: 1.006–1.776), while $PM_{2.5}$ was not related to PTB cases (Figure S5 and Table S4).

Table 3
Associations between a 10 − unit increase in SO_2 or $PM_{2.5}$ and PTB cases in single-pollutant DLNM.

Lag	SO_2		$PM_{2.5}$	
	lag-response	cumulative effect	lag-response	cumulative effect
0	1.201 (1.028–1.403) *	1.201 (1.028–1.403) *	0.979 (0.844–1.136)	0.979 (0.844–1.136)
1	1.185 (1.026–1.367) *	1.423 (1.055–1.919) *	0.998 (0.884–1.126)	0.977 (0.747–1.279)
2	1.168 (1.024–1.333) *	1.662 (1.081–2.557) *	1.014 (0.918–1.119)	0.991 (0.687–1.428)
3	1.152 (1.021–1.301) *	1.915 (1.104–3.323) *	1.027 (0.946–1.115)	1.017 (0.653–1.585)
4	1.136 (1.017–1.269) *	2.176 (1.124–4.213) *	1.038 (0.966–1.114)	1.056 (0.637–1.748)
5	1.120 (1.012–1.240) *	2.438 (1.141–5.211) *	1.046 (0.979–1.116)	1.104 (0.634–1.920)
6	1.105 (1.007–1.213) *	2.694 (1.153–6.293) *	1.051 (0.986–1.120)	1.159 (0.640–2.101)
7	1.090 (1.000-1.188)	2.936 (1.161–7.423) *	1.053 (0.987–1.123)	1.221 (0.650–2.291)
8	1.075 (0.991–1.165)	3.155 (1.163–8.559) *	1.052 (0.985–1.124)	1.284 (0.663–2.489)
9	1.060 (0.981–1.145)	3.344 (1.158–9.654) *	1.049 (0.981–1.121)	1.347 (0.674–2.691)
10	1.045 (0.968–1.129)	3.496 (1.146–10.66) *	1.042 (0.976–1.113)	1.404 (0.682–2.890)
11	1.031 (0.953–1.115)	3.603 (1.125–11.54) *	1.033 (0.969–1.101)	1.450 (0.684–3.076)
12	1.017 (0.936–1.104)	3.663 (1.094–12.26) *	1.021 (0.961–1.085)	1.481 (0.678–3.236)
13	1.003 (0.918–1.095)	3.672 (1.052–12.81) *	1.007 (0.950–1.067)	1.491 (0.663–3.352)
14	0.989 (0.898–1.088)	3.631 (1.000-13.18)	0.990 (0.935–1.048)	1.476 (0.639–3.410)
15	0.975 (0.878–1.083)	3.540 (0.937–13.37)	0.970 (0.914–1.030)	1.432 (0.603–3.399)

Data are shown as RR (95% CI). *, $P < 0.05$.

Lag	SO_2		$PM_{2.5}$	
	lag-response	cumulative effect	lag-response	cumulative effect
16	0.962 (0.857–1.078)	3.404 (0.863–13.42)	0.949 (0.886–1.016)	1.359 (0.557–3.313)
17	0.948 (0.837–1.075)	3.228 (0.781–13.34)	0.925 (0.851–1.006)	1.257 (0.500-3.158)
18	0.935 (0.816–1.072)	3.019 (0.692–13.17)	0.900 (0.810–0.999) *	1.131 (0.433–2.951)
Data are shown as RR (95% CI). *, P < 0.05.				

In sensitivity analyses, we changed the degrees of freedom (1, 2, and 4–8 df) in the "ns" function of humidity and wind speed in GLM, and the results were consistent, that only SO_2 was positively associated with PTB cases (Table S5). We also changed the maximum lag of 18 months to 12 or 6 months in SO_2-$PM_{2.5}$ multi-pollutant DLNM and found only SO_2 was the risk factor of PTB cases (Table S6 and S7).

Discussion

We here showed a positive association between PTB cases in HIV-infected patients and SO_2, but not other air pollutants. The median CD4 cell count of enrolled HIV-infected patients was as low as 57 cells/μL, representing a population highly susceptible to Mycobacterium tuberculosis (10). During the study period, Guangzhou city experienced a marked improvement in air quality due to practical measures including reduction of industrial coal-burning use, controlling volatile organic compounds, and elimination of outdated vehicles (35). The concentrations of three major air pollutants, $PM_{2.5}$, SO_2, and CO, were significantly decreased, whereas the levels of NO_2 and O_3 remained similar between 2014 and 2019 (Table S1). According to Guangzhou Centers for Disease Control and Prevention (CDC) reports, the registered smear-positive tuberculosis cases in Guangzhou decreased from 5022 in 2014 to 3274 in 2019 (36), but the dynamic change of PTB in HIV-infected patients was not clear. Given that more than 80% of local HIV-infected patients had been admitted to Guangzhou Eighth People's Hospital during the study period (23), we here used the hospitalized PTB cases as a substitute to explore the potential link between PTB cases in HIV-infected patients and air pollutants. The number of admitted PTB cases in HIV-infected patients was significantly decreased over time despite a concurrent increasing trend of HIV admission (Figure S1A). In preliminary analyses, there were similar monthly kinetics, which remained stable every month, and positive correlations between SO_2, PTB cases and incidence (Figure S1 and S2). In contrast, $PM_{2.5}$ had a distinct V-shaped monthly kinetics curve and was only weakly correlated to incidence ($r = 0.21$, $P = 0.022$), and other air pollutants were not significantly correlated with PTB cases or incidence (Figure S2). The results for SO_2 in GLM and DLNM were consistent and indicated its positive association with PTB cases within lag 0–3 months (Table S4). Previous Bayesian spatial-temporal studies reported

that SO_2 was associated with PTB cases among the general population within lag 0–1 month (37). Here, we showed that SO_2 remained the specific risk factor of PTB in HIV-infected patients, although a causal relationship between them requires further investigation.

As mentioned above, the role of SO_2 in PTB among the immune-competent population remains controversial and mixed results were reported (19, 21). Nevertheless, there was limited research focused on HIV-infected patients, and a retrospective study conducted in Spain proposed protective effect of short term exposure to SO_2 (1.5 weeks before) on PTB hospitalizations among them (22). In contrast, we here identified SO_2 as the most important environmental risk factor for PTB in this immune-compromised population. This discrepancy might be explained by distinct geographical regions, climates, air pollutants concentrations, and immune statuses of HIV-infected patients, e.g., in the previous study only 30%-40% of patients had CD4 cell counts less than 200 cells/μL (22), while the median CD4 cells of our cohort were as low as 57 cells/μL (Table 1). Since neither the summary statistics nor kinetics curve of air pollutants was reported (22), it seems difficult to interpret different results between studies. Besides, to our knowledge, this is the first study to evaluate the long term effect of SO_2 on PTB in HIV-infected patients, and we also showed a cumulative adverse effect of ambient SO_2.

The mechanism by which SO_2 damages respiratory system is not fully understood, and includes obstructions and hyperreactivity of airway, bronchitis, acute neutrophilic inflammation, and upregulation of pro-fibrotic cytokines (38). When SO_2 dissolves in water, it forms sulfuric acid, which may aggravate airway inflammation and facilitate bacterial infections, e.g., PTB. Although some studies suggest a protective role of low levels of SO_2 in PTB development (21), the cut-off value for health effect and related rationale are not adequately investigated. Furthermore, to date the biological effect of SO_2 in the co-infections of Mycobacterium tuberculosis and HIV remains elusive and warrants more studies. The primary anthropogenic source of SO_2 is burning of fossil fuels for domestic heating, power generation, and motor vehicles. In this study, we showed that HIV-infected patients likely benefit from the decrease of this major air pollutant due to effective controlling measures taken by the government.

This study includes several limitations. Firstly, this was a retrospective, monocenter study although a majority of local HIV-infected patients were enrolled. Secondly, the socio-economic factor was not taken into account. Gross domestic product (GDP) per capita in Guangzhou continuously increased during the study period, likely also contributing to the decrease of PTB cases. Besides, most of the study subjects in our cohort were male (84.8%). Due to a small number of female patients, we did not conduct a stratification study for them. Finally, extrapulmonary tuberculosis, which is also prevalent in HIV-infected patients, was not studied.

Conclusions

In summary, our study revealed a critical role for SO_2 in PTB among HIV-infected patients, providing clues for a deeper understanding of the epidemiology and pathogenesis of this contagious disease in the

context of HIV co-infection.

List Of Abbreviations

human immunodeficiency virus, HIV; acquired immune deficiency syndrome, AIDS; coronavirus disease 2019, COVID-19; pulmonary tuberculosis, PTB; fine particulate, $PM_{2.5}$; sulfur dioxide, SO_2; carbon monoxide, CO; nitrogen dioxide, NO_2; ozone, O_3; relative risk, RR; confidence interval, CI; generalized linear model, GLM; distributed lag non-linear model, DLNM.

Declarations

Ethics approval and consent to participate

The study design was approved by the Ethics Committee of Guangzhou Eighth People's Hospital. The individual identifiers were not used here, so informed consent was not specifically required.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Finding

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Authors' contributions

KD conceived the study and supervised all aspects of the study. YW collected the data.

YW, MC, and KD analyzed the data and prepared the manuscript. All authors read and approved the final manuscript.

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Figures

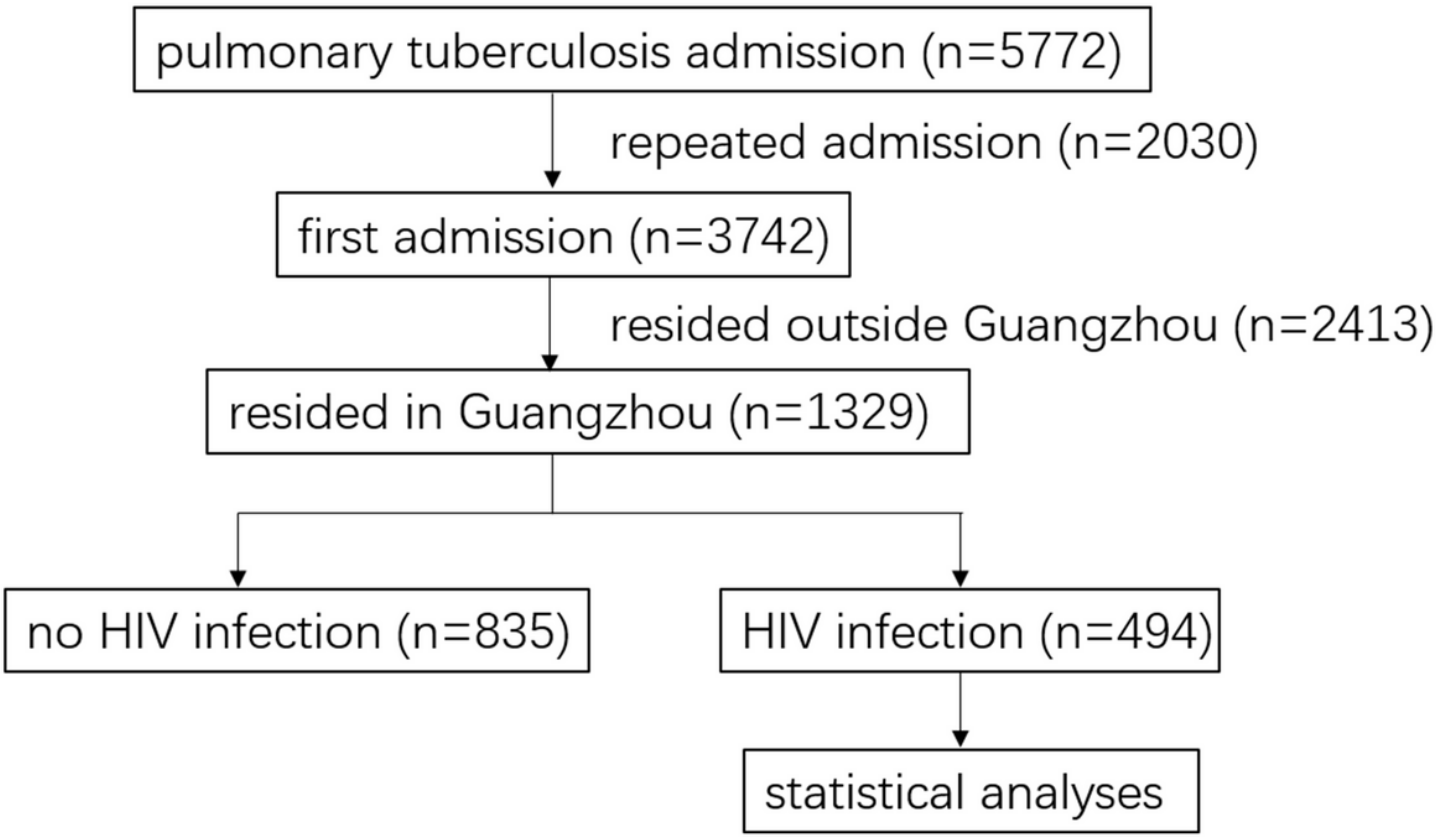

Figure 1

Enrollment of study subjects.

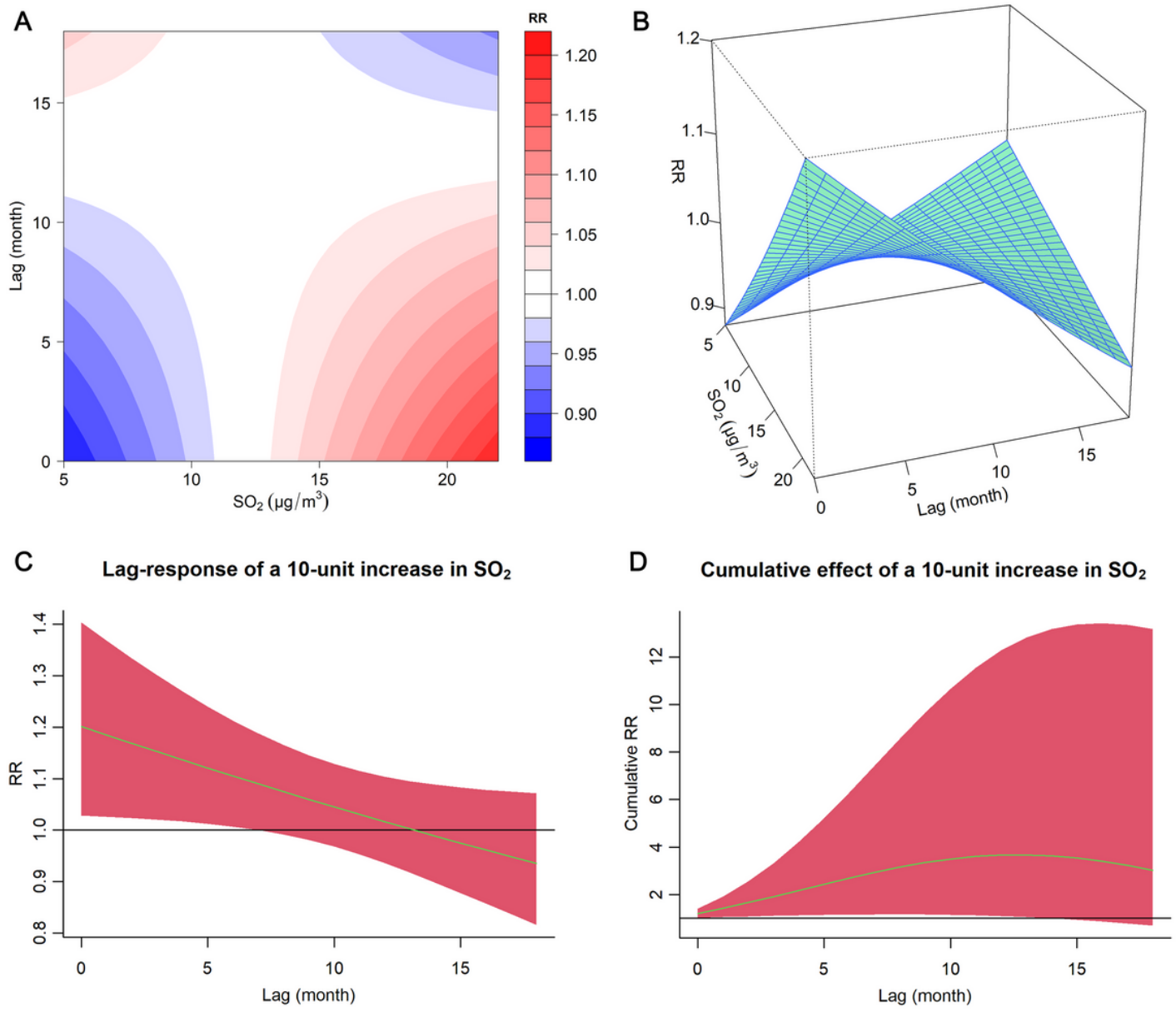

Figure 2

(A) Contour plot of SO_2 effect on PTB. (B) 3D plot of SO_2 effect on PTB. (C) Lag-response curve for a 10-unit increase in SO_2. (D) Cumulative effect of a 10-unit increase in SO_2 on PTB cases. The red shadow indicates 95% confidence interval of RR.

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