**Title:** Effect modification of greenness on PM2.5 associated with all-cause mortality in a multidrug resistant tuberculosis cohort.

**Authors:**

Erjia Ge, Ph.D.

[erjia.ge@utoronto.ca](mailto:erjia.ge@utoronto.ca)

Dalla Lana School of Public Health, University of Toronto, Canada.

Jianhui Gao, MSc.

[jianhui.gao@mail.utoronto.ca](mailto:jianhui.gao@mail.utoronto.ca)

Dalla Lana School of Public Health, University of Toronto, Canada.

Xiaolin Wei, MD. MPH., Ph.D.

Dalla Lana School of Public Health, University of Toronto, Canada.

Zhoupeng Ren, Ph.D.

[renzp@lreis.ac.cn](mailto:renzp@lreis.ac.cn)

State Key Laboratory of Resources and Environmental Information System (LREIS), Institute of Geographic Sciences and Natural Resources Research, Chinese Academy of Sciences, Beijing, China.

Jing Wei, Ph.D.

[weijing\_rs@163.com](mailto:weijing_rs@163.com)

Iowa Technology Institute, Department of Chemical and Biochemical Engineering, The University of Iowa, Iowa City, USA

Xin Liu, MSc.

[liux@lreis.ac.cn](mailto:liux@lreis.ac.cn)

School of Geoscience and Technology, Southwest Petroleum University, Sichuan Province, China.

Xiaomeng Wang, MD, MPH,

[xmwang@cdc.zj.cn](mailto:xmwang@cdc.zj.cn)

Zhejiang Provincial Centre for Disease Control and Prevention, Zhejiang Province, China.

Jieming Zhong, MD, MPH

[jmzhong@cdc.zj.cn](mailto:jmzhong@cdc.zj.cn)

Zhejiang Provincial Centre for Disease Control and Prevention, Zhejiang Province, China.

Jingru Lu, MD.

[ljr630214@sohu.com](mailto:ljr630214@sohu.com)

Institute of Ningxia Tuberculosis Control, The Fourth People’s Hospital of Ningxia.

Xiaomei Tian, MD. MPH

[Txm1227@126.com](mailto:Txm1227@126.com)

Institute of Ningxia Tuberculosis Control, The Fourth People’s Hospital of Ningxia.

Fangrong Fei, MD., MPH

[frfei@cdc.zj.cn](mailto:frfei@cdc.zj.cn)

Zhejiang Provincial Centre for Disease Control and Prevention, Zhejiang Province, China.

Bin Chen, MD, MPH.

[bchen@cdc.zj.cn](mailto:bchen@cdc.zj.cn)

Zhejiang Provincial Centre for Disease Control and Prevention, Zhejiang Province, China.

Xiaolin Wang, MD.

[wxldyj@163.com](mailto:wxldyj@163.com)

Institute of Ningxia Tuberculosis Control, The Fourth People’s Hospital of Ningxia.

Ying Peng\*, MD, MPH,

[ypeng@cdc.zj.cn](mailto:ypeng@cdc.zj.cn)

Zhejiang Provincial Centre for Disease Control and Prevention, Zhejiang Province, China.

Ming Luo\*, Ph.D.

[luom38@mail.sysu.edu.cn](mailto:luom38@mail.sysu.edu.cn)

School of Geography and Planning, Sun Yat-Sen University, Guangdong Province, China.

Juan Lei\*, MD, MPH,

[leijuan.316@163.com](mailto:leijuan.316@163.com)

Institute of Ningxia Tuberculosis Control, The Fourth People’s Hospital of Ningxia.

**\*Corresponding authors**

Address correspondence to Ying Peng, Ming Luo, and Juan Lei.

Ying Peng, MD, MPH

Division of Tuberculosis, Zhejiang Provincial Centre for Disease Control and Prevention,

Address: 3399 Bin Sheng Road, Hangzhou, Zhejiang Province, China.

Email: [ypeng@cdc.zj.cn](mailto:ypeng@cdc.zj.cn)

Tel: +86 671-8711 5188

Fax: +86 571-87115188

Ming Luo, Ph.D.

School of Geography and Planning, Sun Yat-Sen University, Guangdong Province, China.

Room D311, Dihuan Building, Sun Yat-sen University, No. 135 West Xingang Road, Guangzhou

510275, China

[luom38@mail.sysu.edu.cn](mailto:luom38@mail.sysu.edu.cn)

Tel: +86 151 1209 5237

Fax: +86 20-84112593

Juan Lei, MD, MPH

Institute of Ningxia Tuberculosis Control, The Fourth People’s Hospital of Ningxia.

713 Beijing W Rd, Xixia District, Yinchuan, Ningxia, China

[leijuan.316@163.com](mailto:leijuan.316@163.com)

Tel: +86 13895480998

Fax: +86 951-2028278

**Author Contributions**

**Erjia** **Ge** contributed to the conception and designed the study. **Juan Lei, Ying Peng, Xiaomeng Wang, Jieming Zhong, Fangrong Fei, Bin Chen, Jingru Lu, Xiaomei Tian**, and **Xiaolin Wang** collected the MDR-TB cohort data; **Zoupeng Ren, Xin Liu, Ming Luo,** and **Jing Wei** collected and collated NDVI, zPM2.5 and other environmental data; **Erjia Ge** and **Jianhui Gao** conducted statistical analysis; **Erjia Ge** and **Xiaolin Wei** drafted the manuscript; **Ying Peng, Ming Luo,** and **Jing Wei** provided comments and helped interpret results for important intellectual content. All authors reviewed and accepted the final version of the manuscript. z

**Acknowledgement**

This study was supported to **JL** and **YP** by the National Health Commission of China-Bill & Melinda Gates Foundation TB Project (OPP1137180) and the Natural Science Foundation of Ningxia (NZ17219), to **YP** by the Zhejiang Provincial Medical and Health Project (2019RC135) and the State Key Laboratory of Health Technology Assessment, Fudan University (FHTA2019-05), to **BC** by the National Nature Science Foundation of China (71640019), and to **ML** by the Pearl River Talent Recruitment Program of Guangdong Province (2017GC010634).

**Disclaimer**

The funders had no roles in the study design, data collection and analysis, decision on publish, and preparation for the manuscript.

**Running title**

PM2.5, greenness, and mortality in MDR-TB patients.

**Conflict of interest statement**

None declared.

**What is the key question?**

How greenness protects air pollution-related mortality among patients with multidrug resistant tuberculosis (MDR-TB) is completely unknown.

**What is the bottom line?**

Recent experimental and clinical studies suggest that inhalation exposure to PM2.5 impairs important components of the protective human lung and results in suppressing systemic immune response against *M. tuberculosis*, whereas this impact of air pollution may be overstated if greenness was not considered.

**What this study adds to the field**

Consistent with the experimental evidence of oxidative stress and inflammatory effects of PM2.5, our study, the largest MDR-TB cohort, shows that exposure to ambient PM2.5 was significantly associated with risks of mortality among patients with MDR-TB, and highlighted that greenness could benefit patient survival by attenuating the impact of PM2.5.

**Abstract**

**Rationale:** Evidence for the association between fine particulate matter (PM2.5) and mortality among tuberculosis (TB) patients is limited. Whether greenness protects air pollution-related mortality among patients with multidrug-resistant tuberculosis (MDR-TB) is completely unknown.

**Methods:** 2,305 patients reported in Zhejiang and Ningxia were followed from MDR-TB diagnosis until death, loss to follow-up, or end of the study (31 December 2019), with an average follow-up of 1,724 days per patient. 16-day averages of contemporaneous Normalized Difference Vegetation Index (NDVI) in the 500 m buffer of patient’s residence, annual average PM2.5, and estimated oxidant capacity Ox were assigned to patients regarding their geocoded home addresses. Cox proportional hazards regression models were used to estimate hazard ratios per 10 μg/m3 exposure to PM2.5 and all-cause mortality among the cohort and individuals across the three tertiles, adjusting for potential covariates.

**Results:** Hazard ratios (HRs) of 1.702 (95% CI, 1.680-1.725) and 1.169 (1.162-1.175) were observed for PM2.5 associated with mortality for the full cohort and individuals with the greatest tertile of NDVI. Exposures to PM2.5 were stronger in association with mortality for younger patients [HR: 2.434 (2.432-2.435)], female [2.209 (1.874-2.845)], patients in rural [1.780 (1.731-1.829)], and from Ningxia [1.221 (1.078-1.385)]. Cumulative exposures increased the HRs of PM2.5-related mortality, while greater greenness flattened the risk with HRs reduced in 0.188-0.194 on average.

**Conclusions:** Individuals with MDR-TB could benefit from greenness by having attenuated associations between PM2.5 and mortality. Improving greener space and air quality may contribute to lower the risk of mortality from TB/MDR-TB and other diseases.

**Key words:**  Multidrug resistant tuberculosis, Air pollution, PM2.5, Greenness, All-cause mortality

**250 words in Abstract**

**3432 words in main text**

**Introduction**

Earlier studies have shown that particular matter (PM) in alveolar macrophages alters *M. tuberculosis-*induced cytokine production in the lung and systemic components, resulting in relative cellular unresponsiveness [1]. Inhalation exposure to PM impairs important components of the protective human lung and results in suppressing systemic immune response against *M. tuberculosis* [2]. A previous California cohort found that living near to high traffic volume and density roads was associated with 3~28% increased risk of death during tuberculosis (TB) treatment, implying adverse impacts of traffic-related air pollution on TB patients [3]. A recent systematic review suggested that long-term exposure to air pollution could increase infections with *M. tuberculosis*, development of active TB, and TB-related mortality, while these associations are inconsistent due to the small number of the studies [4].

While a number of studies have examined the associations between air pollution and infections with TB and transmissions [5, 6], few have investigated the impacts of PM2.5 exposure on mortality after TB infections. Furthermore, fewer have examined the impacts on multidrug-resistant tuberculosis (MDR-TB), a serious form of TB caused by bacteria that do not respond to isoniazid (INH) and rifampicin (RMP), the two most powerful first-line anti-TB drugs. One previous study on a small Chinese cohort of 752 patients reported the association between air pollution and drug-resistant TB development [7]. However, it has been noted that the impact of air pollution may be overstated if greenness, which is generally thought to affect health through multiple mechanisms, such as mitigating exposures to air pollution, cooling weather, and reducing mental and psychologic stress [8], was not taken into account [9, 10]. Thus, a gap in evidence exists on current studies of how greenness may modify the impact of air pollution on mortality after getting MDR-TB.

We aim to examine the role of residential greenness in modifying the association between chronic PM2.5 exposure and all-cause mortality in a large Chinese MDR-TB cohort across Zhejiang and Ningxia. These two provinces, representing an affluent southeast and a deprived northwest province, respectively, of China, were involved in the National Health Commission of China-Bill and Melinda Gates Foundation TB Collaboration project [11], which was initiated in 2009 and employed innovative molecular tests for TB and MDR-TB, and implemented effective follow-up strategies to delivery and manage patients [12]. We present the associations for the full cohort and across tertiles of greenness measured within 500 meters around patient’s residence during 11 years of follow-up (2009 to 2019), respectively. Oxidant capacity (Ox) is incorporated in our models as previous studies showed that they were associated with more chronic health outcomes, like TB, than either O3 or NO2 alone [13, 14].

We hypothesize that living in greener areas attenuated the risk of PM2.5-related mortality among patients with MDR-TB by potentially increasing exposure to fresh air, lowering emissions, and cooling air.

**Methods**

***The Study cohort***

All MDR-TB cases included in this study were microbiologically confirmed by prefecture-level reference laboratories under rigorous quality control by the Zhejiang Provincial Center for Disease Control and Prevention (CDC) and the Fourth People’s Hospital of Ningxia. Patients were required to provide three sputum samples and drug susceptible testing (DST) at one of the prefecture-level TB-designated hospitals. All the three samples were tested using microscopy, and two were sent for Löwenstein-Jensen solid culture. Culture-positive samples were subject to DST against the first-line anti-TB drug RMP, INH, ethambutol, and streptomycin. Both provinces adopted the case diagnosis and detection procedure recommended by the National Health Commission of China-Bill and Melinda Gates Foundation TB Collaboration project [11].

Active MDR-TB cases reported from January 1st 2009 to December 31st 2017 were eligible for inclusion. We enrolled all confirmed cases diagnosed between January 1st 2009 and December 31st 2017 in Zhejiang and between January 1st 2015 and December 31st 2017 in Ningxia because earlier cases were not available. We excluded migrant patients to reduce exposure misclassification as they might return to hometowns during TB treatment which were not recorded. We also excluded patients who had no complete record of MDR-TB diagnosis, died, moved out of the provinces before diagnosis, or had no air pollution and greenness data available for their residential addresses.

**Measures**

***Outcome measures***

MDR-TB patients were registered and prospectively followed by the Zhejiang Provincial CDC and the Fourth People’s Hospital of Ningxia from diagnosis confirmation to death, loss to follow-up, or end of the study by December 31st, 2019. We verified mortality information through the vital registration database obtained in both provincial CDCs.

***Exposure measures***

We assigned estimates of air pollution and greenness exposures to patients from date of MDR-TB confirmed to either date of death, loss to follow-up, or the end of the study by geocoding patients’ home addresses (Figure 1). The detailed geocode method was described and verified in our previous studies [15].

***Pollutants***

High-resolution (1 km) annual PM2.5 was from the space-time extremely randomized trees model that integrated total column aerosol depth retrievals from the Moderate Resolution Imaging Spectroradiometer (MODIS) of the National Aeronautics and Space Administration (NASA) ’s Terra and Aqua satellite [16, 17]. The annual PM2.5 were synthesized from the daily PM2.5 data of MODIS AOD and a large number of auxiliary data, including meteorological conditions, human distribution, and pollution emission, using the method proposed in our previous study [16]. The estimated annual mean PM2.5 were highly consistent the ground-based measurements with a high correlation coefficient (*R*2 = 0.94) in China [17]. Additionally, we calculated the combined oxidant capacity (Ox) of O3 and NO2 as a weighted average with weights equivalent to their respective redox potentials (i.e. Ox = [(1.07 x NO2) + (2.075 x O3)]/3.145) [18]. Daily NO2 and O3 were obtained from the National Air Quality Network of the Chinese Ministry of Environmental Protection. The annual concentrations of NO2 were derived from a temporally adjusted national land-use regression model that combined 1,500 fixed-site nationwide monitoring data, satellite NO2 estimates, road length within 10 km, industrial land-use areas within various buffers and meteorological factors [19]. Ozone exposures were estimated based on eight-hour average daily maximum concentrations by integrating monitoring O3 with the surface temperature, relative humidity, wind speed and direction, land-use areas, and various anthropogenic emissions using the Weather Research and Forecasting atmospheric chemistry (WRF-Chem) models [20]. In our model, NO2 and O3 were not included to reduce multilinearities with PM2.5 and Ox.

***Greenness***

The Normalized Difference Vegetation Index (NDVI) has been used in measuring greenness exposure in epidemiological studies [21, 22]. NDVI values range from -1 to +1, with -1 for water, 0 for bare soil, and +1 for healthy vegetation [23]. 16-day average greenness surface data at 500 m500 m were derived from MODIS for the study period. The dataset has been used and verified by other studies [9, 21, 22]. We calculated the cumulative 16-day average NDVI values based on the method introduced in [21] and linked NDVI to patient from diagnosis confirmation to death, loss to follow-up, or end of follow-up according to the patient’s home address.

Map

Description automatically generated

Figure 1. Characteristics of MDR-TB distribution and greenness (i.e. NDVI) in (a) Ningxia and (b) Zhejiang, China.

***Covariates***

There were three domains of covariates collected by this study: patient’s individual characteristics, treatment, and environment: individual characteristics include age at diagnosis, sex, occupation, ethnicity; covariates related to treatment include drug-resistant type (i.e. MDR, or extensively drug-resistant (XDR) TB), if the patient took MDR-TB treatments or not, and if the case had TB-related treatment before the diagnosis of MDR-TB (suggesting acquired resistance) or the case was initially diagnosed as MDR-TB without any TB treatment before (suggesting primary resistance) [24, 25]; covariates related to environment include province (i.e. Zhejiang or Ningxia), place of residence (i.e. urban or rural), altitude as a proxy for meteorological factors, like temperature, monthly average nighttime light index (NTL) as a proxy for socio-economic and urbanization levels. NTL derived from satellite images represents light intensity level at night with values ranging from 0 to 63, with higher values indicating brighter light. The altitude and monthly NTL were publicly available from the NASA’s Socioeconomic Data and Applications Center with details about NTL data can be found in [26]. The monthly average NTL values were also calculated and linked patients during the follow-up according to their home addresses.

***Statistical analysis***

The number and proportion of MDR-TB patients were stratified by individual characteristics, treatment history, and environment where they live across tertiles of NDVI. The association between PM2.5 and mortality was assessed using the Cox proportional hazards regression model with Ox adjusted for the full cohort and the three tertiles, separately. Hazard ratios were calculated per 10 μg/m3 and presented with 95% confidence intervals. The three domains of covariates were included in multivariable Cox proportional hazard regression models to adjust for potential confounding. We used the plots of the Martingale-based residuals to check violation of the proportional hazard assumption [27]. Covariates that could not meet the proportional hazards assumption were excluded from the regression.

Sensitivity analyses were implemented through a series subgroup tests for the effect modification by age, sex, treatment (treated vs untreated, primary resistance vs acquired resistance), living areas (urban vs rural), and province (Zhejiang vs. Ningxia). We fitted separate multivariable Cox models for groups and reported the strata-specific effects at a p-value < 0.05.

We examined the linearity of exposure-response relationships for the full cohort and the three tertiles of NDVI using the cubic regression spline [28]. Additionally, statistical tests were further conducted to examine if the HRs were significantly different in the three different tertiles and if the risk of PM2.5-related mortality was lower for the patients with greater greenness. All the statistical analyses were carried out using *R* v.3.5.3 with the ‘survival’ package.

***Ethics approval***

This study was reviewed and approved by the ethics review board at the Zhejiang Provincial Center for Disease Control Prevention. Informed consent was not required because this study relied on existing public health records other than on direct patient contact, and all personal identifiers were removed from the database before analyses.

**Results**

After excluding 443 (15.4%) migrant patients and 10 (0.35%) local patients who did not have complete residential information or no air pollution or NDVI data, we included 2,305 MDR-TB cases with 2,095 from Zhejiang and 210 from Ningxia in the study. All patients were reported between 2009 and 2017, and followed to December 31st, 2019, with an average follow-up of 1,724 days per patient. Among the patients, there were 525 deaths during the period of follow-up.

***Descriptive statistics***

Of 2,305 cases, 1,674 (72.6%) were male, 62 (2.69%) were ethnic minority, 641 (27.8%) were 60 years and older at diagnosis, and 37 (1.61%) were XDR-TB. Prior to MDR-TB diagnosis, 1,535 (66.6%) had no received any TB treatment indicating primary resistance, while 770 (33.4%) were treated indicating acquired resistance. Of all patients, 1,716 (74.4%) received MDR-TB treatment, while 589 (25.6%) did not take the treatment (Table 1). A higher proportion of MDR-TB patients lived in rural (74.2%), low altitude (≤200m, 81%) areas. Approximately 20% patients worked indoors, while 12% were engaged in intelligent-intensive work.

--- Insert Table 1. ---

***Mean levels of exposures***

Table 2. shows the mean distribution of NDVI, PM2.5, and Ox associated with individuals in the full cohort and across the three tertiles of greenness (NDVI, T1: 0.008 to 0.275, T2: 0.276 to 0.408, T3: 0.409 to 0.850) within 500m buffer of patient’s residence. There were 692, 691, and 922 patients in the three tertiles, respectively. The mean NDVI increases over the three tertiles (NDVI: T1: 0.22, T2, 0.33, T3: 0.55), whereas the mean of PM2.5 and Ox declines (PM2.5, T1: 48.4 μg/m3, T2: 45.4 μg/m3, T3: 41.2μg/m3; Ox: T1: 78.3 μg/m3, T2: 77.4 μg/m3, T3: 75.1 μg/m3). NDVI is moderately negatively associated with PM2.5 (*p* = - 0.34) and Ox (*p* = - 0.32), while the correlation between PM2.5 and Ox is positive and relatively stronger (*p* = 0.63) during the follow-up (Figure 2).

--- Insert Table 2. ---

Chart, histogram

Description automatically generated

Figure 2. Correlations among exposures variables (NDVI, PM2.5, and Ox) for the 2,305 patients with complete covariates. NDVI = normalized difference vegetation index. PM2.5 = fine particulate matter. Ox = Oxidant capacity (Ox = [(1.07 x NO2) + (2.075 x O3)]/3.145).

***Hazard ratios from Cox regression models***

Table 3 shows the results of single- and oxidant-pollutant adjusted Cox proportional hazards regression models. All regression models were fully adjusted for individual characteristics, treatment, and environmental factors (detailed in the Methods section). Exposure to PM2.5 was significantly associated with mortality in both single- (HR: 1.581, 95% CI: 1.567-1.595 per 10 μg/m3 increase in PM2.5) and oxidant-pollutant models (HR: 1.702, 95% CI: 1.680-1.725) for the full cohort. The effect modifications by greenness were slightly stronger for untreated (HR: 1.498, 95% CI: 1.476-1.521) than treated patients (HR: 1.660, 95% CI: 1.620-1.700), and for those who obtained MDR-TB through primary resistance (HR: 1.453, 95% CI: 1.421-1.486) than through acquired resistance (HR: 1.638, 95% CI: 1.623-1.654) in single-pollutant models. Similar associations were observed adjusting for Ox in oxidant-pollutant models. Consistent with previous studies [10], we did not find a monotonic trend in the effect of PM2.5 within the different tertiles of NDVI: the mortality risks were lowered in the greatest tertile of NDVI than those in the other two tertiles in both models for the full cohort and other groups, except for the treated patient group in single-pollutant model.

--- Insert Table 3. ---

We repeated the oxidant-pollutant adjusted models to examine the association stratified by age (< 60 and ≥ 60 years old), sex, place of residence (urban and rural), and province (Zhejiang and Ningxia). Table 4 showed the stratified analysis results, suggesting that exposure to PM2.5 were stronger in association with mortality for younger patients [HR: 2.434, 95% CI: 2.432-2.435 (< 60 years) vs HR: 1.487, 95% CI: 1.475-1.501 (≥ 60 years)], female [HR: 2.209, 95% CI: 1.874-2.845 (female) vs HR: 1.644, 95% CI: 1.611-1.678 (male)], and patients from Ningxia province [HR: 1.221, 95% CI: 1.078-1.385 (Ningxia) vs HR: 1.059, 95% CI: 1.049-1.069 (Zhejiang)]. For patients living in rural, the hazard ratio (HR) was 1.780 [95% CI: 1.731-1.829] slightly higher than those living in urban areas [HR: 1.739, 95% CI: 1.631-1.854]. Exposure to PM2.5 in the lower greenness showed a trend of increasing mortality risk for older (≥ 60 years old), male, and patients living in urban areas and Zhejiang province. We did not observe a similar increasing trend among patients in Ningxia due to very limited cases in this tertile.

***Exposure-response curves***

The exposure-response curves shown in Figure 3 suggested non-linearity in the association between PM2.5 exposure and mortality among MDR-TB patients for the full cohort (Figure 3a) and the three tertiles (Figure 3b, 3c, and 3d) of NDVI, within the 500m buffer around patient’s residence. Cumulative exposures increased the hazard ratios of PM2.5-related mortality, while greater greenness substantially flattened the risk with the HRs reduced in 0.188 (95% CI, 0.123, 0.253) (tertile 2, Figure 3c) to 0.194 (95% CI, 0.129, 0.259) (tertile 3, Figure 3d) on average, compared to the lowest greenness (tertile 1, Figure 3b).

Chart

Description automatically generated

Figure 3. Association curves (in red) with 95% confidence intervals (in light blue) for annual mean PM2.5 and mortality for (a) the full cohort of 2,305 MDR-TB patients and individuals under different tertiles of contemporaneous NDVI: (b) Tertile 1 of contemporaneous NDVI. (c) Tertile 2 of contemporaneous NDVI. (c) Tertile 3 of contemporaneous NDVI. Through the ANOVA test and the calculation of the Tukey Honest Significant Differences, we found that the HRs of tertials 2 and 3 were 0.194 (95% CI, 0.129, 0.259) and 0.188 (95% CI, 0.123, 0.253) lower than that of tertile 1 on average. HR = Hazard ratio. NDVI = normalized difference vegetation index. PM2.5 = fine particulate matter.

**Discussion**

To our knowledge, this study represents the largest population-based study of MDR-TB in China with 11 years of follow-up. Although MDR-TB is treatable and curable with second-line drugs, the disease has high mortality, responsible for an estimate of 2.5 million deaths globally by 2050 if no interventions [29]. Inhaled PM was noted relevant to TB infection and transmission [30–32], while evidence regarding the impacts of PM2.5 on mortality among TB patients is still sparse. Furthermore, fewer have examined for MDR-TB and how greenness modifies the risk of PM2.5-related mortality. Our study found a 70.2% increase in mortality per 10 μg/m3 increase in PM2.5 exposure, after adjusting for Ox, in the full MDR-TB cohort. Greater exposure to greenness lowered the impacts of PM2.5 for untreated and primary resistance patient groups, except those taking MDR-TB treatment. Our data suggested that living in lower greenery neighborhoods increased risks of mortality associated with PM2.5, particularly in elderly (≥ 60 years), male, and patients from urban areas, while it did not show that greenness attenuated the effect of PM2.5 in the province of Ningxia. These findings are important because they examined the effects of inhaled PM on mortality after infecting with MDR-TB and the effect modification by greenness, which are still unclear to us.

Our study provides reliable exposure measurements as we excluded migrant patients and permanent resident patients without residential information, air pollutant or NDVI data. All 2,305 patients included in the analyses have permanent home addresses registered in the TB surveillance systems of the provincial CDC. Our results showed that the associations between PM2.5 and mortality were consistent for both the full cohort and the three different greenness levels as well.

The adverse effects of ambient PM2.5 against TB/MDR-TB are biologically plausible. Air pollution has detrimental impact on lung function and immune system through decreasing macrophage functioning, promoting oxidative stress and inflammation, and increasing reactivity and enhanced vulnerability towards pathogens [33, 34]. The oxidative stress caused by PM could damage the epithelium of the airways and reduce immune response against *M. tuberculosis* [1, 35]*.*  Inflammation induction and particle deposits in the damaged lungs could cause further reduction of pulmonary function and promote disease progression and deaths, particularly MDR-TB patients. A Chinese cohort found that exposure to PM2.5 was associated with a 30% increase in the risks of all-cause mortality and 72% increase in the deaths from TB, respectively [36]. Our risk estimates of exposure to PM2.5 and all-cause mortality for the full cohort of MDR-TB patients was higher, suggesting that MDR-TB patients might be more vulnerable to ambient PM than those with a regular TB.

*Ji et al.* [10] used a prospective cohort of 12,873 participants from 631 cities and counties in 22 Chinese provinces to measure whether greenness protects against air pollution-related mortality between 2008 and 2014. This large-scale longitudinal study found that increasing greenness exposure could reduce mortality associated with PM2.5 exposure in the 500m radium around participant’s residence. Although no studies have examined the effect modification by greenness among TB or MDR-TB patients, *Ji et al.*’s estimates of greenness in reducing risks of all-cause mortality relevant to PM2.5 are consistent with our findings.

*Crouse et al.* [9] conducted a larger cohort study that includes 2.4 million non-immigrant Canadians to examine the role of residential greenness in modifying associations between chronic PM2.5 exposure and non-accidental mortality during 11 years of follow-up. They found that individuals in deprived neighborhoods with high greenness benefitted by having more attenuated associations between PM2.5 and mortality than those living in deprived areas with less greenness. Our study observed greater benefits for patients in urban with higher greenness level than those in urban with less greenness, but not for those in rural areas.

Some previous studies suggested that differences in sex and age regarding the impacts of greenness on PM2.5 associated with mortality [10, 37]. However, the literature has been inconsistent. Our observed more attenuated risks of mortality relevant to PM2.5 with the greatest greenness among younger (< 60 years), untreated, and primary resistance patients imply that effect heterogeneity exists in age, sex, treatment, and development of drug resistance, although exact mechanisms need to be elucidated.

A strength of this study is its inclusion of all reported MDR-TB patients in Zhejiang and Ningxia, two provinces implemented rigorous diagnosis methods and 24-month standardized treatment under the China-Bill and Melinda Gates TB project. Additionally, we had detailed demographic data, treatment history, and environmental data around patient’s residence, which allow us to conduct full adjusted models and a series stratified analysis. Despite these strengths, a few limitations should be noted. Although migrant and local patients who did not have residential information or nor air pollution/NDVI data were excluded, misclassification (over- or underestimation) and selection, albeit low, might still be possible. Although we have adjusted for a set of potential individual and contextual covariates, which minimized but might not have fully eliminated confounding. For example, some MDR-TB patients received individual adjusted treatment when standardized MDR-TB regimens were not effective; however, we did not have information regarding change of regimens during treatment. Although we have adjusted for potential regional effects and stratified the analyses by the provinces, the hazard ratio of PM2.5 could not be confirmed for only 4 cases in the most greenery areas (i.e., the third tertile of NDVI) of Ningxia given its relatively small population. Different vegetation types might have different abilities in absorbing air pollution [38]. The heterogeneity of the greenness modification effects in the two different provinces could be explained if data on vegetation types were available. Lastly, smoking could adversely affect TB treatment [39] and lower survival among patients with MDR-TB [40], while greenness might attenuate the impact. We could not adjust for smoking as these data were neither available for individuals nor for communities during the follow-up. Future studies should consider adjusting for these potential confounding.

In conclusion, this large MDR-TB cohort study adds evidence of greenness which benefits survival by attenuating the association between PM2.5 and mortality among MDR-TB patients. Improving green space and air quality, along with effective treatments, may contribute to the reduction of mortality for MDR-TB.

**Reference**

1. Torres M, Carranza C, Sarkar S, Gonzalez Y, Osornio Vargas A, Black K, Meng Q, Quintana-Belmares R, Hernandez M, Angeles Garcia JJF, Páramo-Figueroa VH, Iñiguez-Garcia MA, Flores JL, Zhang JJ, Gardner CR, Ohman-Strickland P, Schwander S. Urban airborne particle exposure impairs human lung and blood Mycobacterium tuberculosis immunity. *Thorax* 2019; 74: 675–683.

2. Sarkar S, Rivas-Santiago CE, Ibironke OA, Carranza C, Meng Q, Osornio-Vargas Á, Zhang J, Torres M, Chow JC, Watson JG, Ohman-Strickland P, Schwander S. Season and size of urban particulate matter differentially affect cytotoxicity and human immune responses to Mycobacterium tuberculosis. *PLoS ONE* 2019; 14: e0219122.

3. Blount RJ, Pascopella L, Catanzaro DG, Barry PM, English PB, Segal MR, Flood J, Meltzer D, Jones B, Balmes J, Nahid P. Traffic-Related Air Pollution and All-Cause Mortality during Tuberculosis Treatment in California. *Environ Health Perspect.* 2017; 125(9): 097026-1-11.

4. Popovic I, Soares Magalhaes RJ, Ge E, Marks GB, Dong G-H, Wei X, Knibbs LD. A systematic literature review and critical appraisal of epidemiological studies on outdoor air pollution and tuberculosis outcomes. *Environmental Research* 2019; 170: 33–45.

5. Smith GS, Van Den Eeden SK, Garcia C, Shan J, Baxter R, Herring AH, Richardson DB, Van Rie A, Emch M, Gammon MD. Air Pollution and Pulmonary Tuberculosis: A Nested Case-Control Study among Members of a Northern California Health Plan. *Environ. Health Perspect.* 2016; 124: 761–768.

6. Lai T-C, Chiang C-Y, Wu C-F, Yang S-L, Liu D-P, Chan C-C, Lin H-H. Ambient air pollution and risk of tuberculosis: a cohort study. *Occup Environ Med* BMJ Publishing Group Ltd; 2016; 73: 56–61.

7. Yao L, LiangLiang C, JinYue L, WanMei S, Lili S, YiFan L, HuaiChen L. Ambient air pollution exposures and risk of drug-resistant tuberculosis. *Environment International* 2019; 124: 161–169.

8. Markevych I, Schoierer J, Hartig T, Chudnovsky A, Hystad P, Dzhambov AM, de Vries S, Triguero-Mas M, Brauer M, Nieuwenhuijsen MJ, Lupp G, Richardson EA, Astell-Burt T, Dimitrova D, Feng X, Sadeh M, Standl M, Heinrich J, Fuertes E. Exploring pathways linking greenspace to health: Theoretical and methodological guidance. *Environ. Res.* 2017; 158: 301–317.

9. Crouse DL, Pinault L, Balram A, Brauer M, Burnett RT, Martin RV, van Donkelaar A, Villeneuve PJ, Weichenthal S. Complex relationships between greenness, air pollution, and mortality in a population-based Canadian cohort. *Environment International* 2019; 128: 292–300.

10. Ji JS, Zhu A, Lv Y, Shi X. Interaction between residential greenness and air pollution mortality: analysis of the Chinese Longitudinal Healthy Longevity Survey. *The Lancet Planetary Health* Elsevier; 2020; 4: e107–e115.

11. Chinese Government and Foundation Announce Partnership to Fight Tuberculosis - Bill & Melinda Gates Foundation. Available from: https://www.gatesfoundation.org/Media-Center/Press-Releases/2009/04/Chinese-Government-and-Foundation-Announce-Partnership-to-Fight-Tuberculosis.(Latest access on Jun 16, 2020)

12. Wang N, Li T, Du X, Li Y, Sun M, Huan S, Zhang H, Wang L, Chen M, Huang F, Zhao Y. Effectiveness of the Integrated TB Surveillance System — China, 2018–2019. China CDC Weekly; 2020; 2 (12): 190–193.

13. Weichenthal S, Pinault LL, Burnett RT. Impact of Oxidant Gases on the Relationship between Outdoor Fine Particulate Air Pollution and Nonaccidental, Cardiovascular, and Respiratory Mortality. *Scientific Reports*; 2017; 7: 16401.

14. Williams ML, Atkinson RW, Anderson HR, Kelly FJ. Associations between daily mortality in London and combined oxidant capacity, ozone and nitrogen dioxide. *Air Qual Atmos Health* 2014; 7: 407–414.

15. Ge E, Zhang X, Wang X, Wei X. Spatial and temporal analysis of tuberculosis in Zhejiang Province, China, 2009-2012. *Infect Dis Poverty* 2016; 5 (11), *doi*: 10.1186/s40249-016-0104-2.

16. Wei J, Li Z, Cribb M, Huang W, Xue W, Sun L, Guo J, Peng Y, Li J, Lyapustin A, Liu L, Wu H, Song Y. Improved 1km resolution PM2.5 estimates across China using enhanced space–time extremely randomized trees. *Atmos. Chem. Phys.* 2020; 20: 3273–3289.17.

17. Wei J, Li Z, Lyapustin A, Sun L, Peng Y, Xue W, Su T, Cribb M. Reconstructing 1-km-resolution high-quality PM2.5 data records from 2000 to 2018 in China: spatiotemporal variations and policy implications. *Remote Sensing of Environment* 2021; 252: 112–136.

18. Bratsch SG. Standard Electrode Potentials and Temperature Coefficients in Water at 298.15 K. *Journal of Physical and Chemical Reference Data* 1989; 18: 1–21.

19. Liu M, Lin J, Wang Y, Sun Y, Zheng B, Shao J, Chen L, Zheng Y, Chen J, Fu T-M, Yan Y, Zhang Q, Wu Z. Spatiotemporal variability of NO2 and PM2.5 over Eastern China: observational and model analyses with a novel statistical method. *Atmos. Chem. Phys.* 2018; 18: 12933–12952.

20. Feng T, Bei N, Huang R-J, Cao J, Zhang Q, Zhou W, Tie X, Liu S, Zhang T, Su X, Lei W, Molina LT, Li G. Summertime ozone formation in Xi’an and surrounding areas, China. *Atmos. Chem. Phys.* 2016; 16: 4323-4342.

21. Ji JS, Zhu A, Bai C, Wu C-D, Yan L, Tang S, Zeng Y, James P. Residential greenness and mortality in oldest-old women and men in China: a longitudinal cohort study. *The Lancet Planetary Health* 2019; 3: e17–e25.

22. Banay RF, James P, Hart JE, Kubzansky LD, Spiegelman D, Okereke OI, Spengler JD, Laden F. Greenness and Depression Incidence among Older Women. *Environ Health Perspect* 2019; 127: 027001.

23. Measuring Vegetation (NDVI & EVI). NASA Earth Observatory; 2000. Available from: https://earthobservatory.nasa.gov/features/MeasuringVegetation. (Latest access on Jul 7th, 2020)

24. Yang C, Shen X, Peng Y, Lan R, Zhao Y, Long B, Luo T, Sun G, Li X, Qiao K, Gui X, Wu J, Xu J, Li F, Li D, Liu F, Shen M, Hong J, Mei J, DeRiemer K, Gao Q. Transmission of Mycobacterium tuberculosis in China: A population-based molecular epidemiologic Study. *Clin Infect Dis* 2015; 61: 219–227.

25. Yang C, Luo T, Shen X, Wu J, Gan M, Xu P, Wu Z, Lin S, Tian J, Liu Q, Yuan Z, Mei J, DeRiemer K, Gao Q. Transmission of multidrug-resistant Mycobacterium tuberculosis in Shanghai, China: a retrospective observational study using whole-genome sequencing and epidemiological investigation. *The Lancet Infectious Diseases* 2017; 17: 275–284.

26. Earth at Night. NASA Earth Observatory; 2017. Available from: https://earthobservatory.nasa.gov/features/NightLights. (Latest access on Jul 7th, 2020)

27. Lin DY, Wei LJ, Ying Z. Checking the Cox Model with Cumulative Sums of Martingale-Based Residuals. *Biometrika* 1993; 80: 557–572.

28. Harrell F. Regression modeling strategies with applications to linear models, logistic regression and survival analysis. New York, NY: Springer-Verlag; 2001.

29. The Economist. It’s Time to End Drug-Resistant Tuberculosis: The Case for Action; 2019. Available from: https://www.eiu.com/graphics/marketing/pdf/its-time-to-end-drug-resistant-tuberculosis-full-report.pdf. (Latest access on Jul 7th, 2020)

30. Lin Y-J, Lin H-C, Yang Y-F, Chen C-Y, Ling M-P, Chen S-C, Chen W-Y, You S-H, Lu T-H, Liao C-M. Association between ambient air pollution and elevated risk of tuberculosis development. *Infect Drug Resist* 2019; 12: 3835–3847.

31. Li Z, Mao X, Liu Q, Song H, Ji Y, Xu D, Qiu B, Tian D, Wang J. Long-term effect of exposure to ambient air pollution on the risk of active tuberculosis. *International Journal of Infectious Diseases* 2019; 87: 177–184.

32. Hwang S, Kang S, Lee J-Y, Lee JS, Kim HJ, Han SK, Yim J-J. Impact of outdoor air pollution on the incidence of tuberculosis in the Seoul metropolitan area, South Korea. *Korean J Intern Med* 2014; 29: 183–190.

33. Laumbach RJ, Kipen HM. Respiratory health effects of air pollution: update on biomass smoke and traffic pollution. *J. Allergy Clin. Immunol.* 2012; 129: 3–11; quiz 12–13.

34. Bauer RN, Diaz-Sanchez D, Jaspers I. Effects of air pollutants on innate immunity: the role of Toll-like receptors and nucleotide-binding oligomerization domain-like receptors. *J. Allergy Clin. Immunol.* 2012; 129: 14–24; quiz 25–26.

35. Sarkar S, Song Y, Sarkar S, Kipen HM, Laumbach RJ, Zhang J, Strickland PAO, Gardner CR, Schwander S. Suppression of the NF-κB Pathway by Diesel Exhaust Particles Impairs Human Antimycobacterial Immunity. *The Journal of Immunology* American Association of Immunologists; 2012; 188: 2778–2793.

36. Peng Z, Liu C, Xu B, Kan H, Wang W. Long-term exposure to ambient air pollution and mortality in a Chinese tuberculosis cohort. *Science of The Total Environment* 2017; 580: 1483–1488.

37. Crouse DL, Pinault L, Balram A, Hystad P, Peters PA, Chen H, van Donkelaar A, Martin RV, Ménard R, Robichaud A, Villeneuve PJ. Urban greenness and mortality in Canada’s largest cities: a national cohort study. *The Lancet Planetary Health* 2017; 1: e289–e297.

38. Barwise Y, Kumar P. Designing vegetation barriers for urban air pollution abatement: a practical review for appropriate plant species selection. *npj Clim and Atmos Sci* 2020; 3(12). *doi*: 10.1038/s41612-020-0115-3.

39. Leung CC, Yew WW, Chan CK, Chang KC, Law WS, Lee SN, Tai LB, Leung ECC, Au RKF, Huang SS, Tam CM. Smoking adversely affects treatment response, outcome and relapse in tuberculosis. *European Respiratory Journal* 2015; 45: 738–745.

40. Balabanova Y, Ignatyeva O, Fiebig L, Riekstina V, Danilovits M, Jaama K, Davidaviciene E, Radiulyte B, Popa CM, Nikolayevskyy V, Drobniewski F. Survival of patients with multidrug-resistant TB in Eastern Europe: what makes a difference? *Thorax* 2016; 71: 854–861.

**Tables**

*Table 1. Characteristics of individuals at baseline in the full cohort (n = 2,305) and across tertiles of greenness (i.e. NDVI) within 500m buffer around patient’s residence.*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Greennesstertile\*** | | | |
|  | **Full cohort (range**  **0.008 to 0.850)** | **Tertile 1 (range**  **0.008 to 0.275)** | **Tertile 2 (range**  **0.276 to 0.408)** | **Tertile 3 (range**  **0.409 to 0.850)** |
|  | n(%) | n(%) | n(%) | n(%) |
| All patients | 2,305 (100) | 692 (30.0) | 691 (29.9) | 922 (40.0) |
| **Stratified by sex** |  |  |  |  |
| Male | 1,674 (72.6) | 500 (21.7) | 469 (20.3) | 705 (30.6) |
| Female | 631 (27.4) | 192 (8.33) | 222 (9.63) | 217 (9.41) |
| **Stratified by age (years)** |  |  |  |  |
| 0 − 59 | 1,664 (72.2) | 541 (23.5) | 522 (22.6) | 601 (26.1) |
| ≥ 60 | 641 (27.8) | 151 (6.55) | 169 (7.33) | 321 (13.9) |
| **Stratified by ethnicity** |  |  |  |  |
| Han | 2,243 (97.3) | 652 (28.3) | 670 (29.1) | 921 (40.0) |
| Others | 62 (2.69) | 40 (1.74) | 21 (0.91) | 1 (0.04) |
| **Stratified by drug resistant** |  |  |  |  |
| MDR | 2,268 (98.4) | 680 (29.5) | 689 (29.9) | 899 (39.0) |
| XDR | 37 (1.61) | 19 (0.82) | 11 (0.47) | 7 (0.30) |
| **Stratified by treatments** |  |  |  |  |
| Treated | 1,716 (74.4) | 510 (22.1) | 536 (23.3) | 670 (29.1) |
| Untreated | 589 (25.6) | 182 (7.90) | 155 (6.72) | 252 (10.9) |
| **Stratified by MDR-TB acquirement** |  |  |  |  |
| Primary resistance | 1,535 (66.6) | 424 (18.4) | 458 (19.9) | 653 (28.3) |
| Acquired resistance | 770 (33.4) | 268 (11.6) | 233 (10.1) | 269 (11.7) |
| **Stratified by occupation** |  |  |  |  |
| Labour-intensive | 1,729 (75.0) | 517 (22.4) | 524 (22.7) | 688 (29.8) |
| Intelligent-intensive | 276 (12.0) | 72 (3.12) | 87 (3.77) | 117 (5.08) |
| **Stratified by working environment** |  |  |  |  |
| Indoor | 457 (19.8) | 125 (5.42) | 144 (6.24) | 118 (5.12) |
| Outdoor | 1,548 (67.2) | 464 (26.8) | 467 (20.3) | 617 (20.1) |
| **Stratified by region** |  |  |  |  |
| Urban area | 595 (25.8) | 150 (6.51) | 166 (7.20) | 279 (12.1) |
| Rural area | 1,710 (74.2) | 542 (23.5) | 525 (22.8) | 643 (27.9) |
| **Altitude**† |  |  |  |  |
| High altitude (*>* 200 m) | 437 (19.0) | 124 (5.38) | 86 (3.73) | 227 (9.85) |
| Low altitude (≤ 200 m) | 1,868 (81.0) | 568 (24.6) | 605 (26.2) | 695 (30.2) |
| **Stratified by Province** |  |  |  |  |
| Ningxia | 210 (9.10) | 123 (5.34) | 83 (3.60) | 4 (0.17) |
| Zhejiang | 2,095 (90.9) | 569 (24.7) | 608 (26.4) | 918 (39.8) |
| **Nighttime Light** **(NTL)**‡ |  |  |  |  |
| High NTL | 1,152 (50.0) | 596 (25.9) | 458 (19.9) | 98 (4.25) |
| Low NTL | 1,153 (50.0) | 96 (4.16) | 233 (10.1) | 824 (3.57) |

\*Greenness exposure is defined as 16-day average NDVI within 500m buffer around patient’s residence address during

follow-up, dividing into tertiles.

† Altitude as proxy for meteorological factors, using the mean value of 200 meters as the low-high cutoff.

‡ NTL: nighttime light index as proxy for socio-economic and urbanization level, using the median value of 6.42 as the

low-high cutoff.

*Table 2. Baseline characteristics by NDVI, PM2.5 (µg/m3), and Ox (ppb)assigned to individuals in the full cohort (n = 2,305) and across the three tertiles of greenness (i.e. NDVI) within 500m buffer around patient’s residence.*

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Full cohort (range 0.008 to 0.850)** | | | **Tertile 1 (range 0.008 to 0.275)** | | | **Tertile 2 (range 0.276 to 0.408)** | | | **Tertile 3 (range 0.409 to 0.850)** | | |
|  | **NDVI** | **PM**2.5 | **O***x* | **NDVI** | **PM**2.5 | **O***x* | **NDVI** | **PM**2.5 | **O***x* | **NDVI** | **PM**2.5 | **O***x* |
| **Mean** | 0.39 | 44.6 | 76.8 | 0.22 | 48.4 | 78.3 | 0.33 | 45.4 | 77.4 | 0.55 | 41.2 | 75.1 |
| **Standard deviation** | 0.15 | 11.0 | 5.02 | 0.04 | 11.9 | 4.79 | 0.04 | 9.90 | 4.98 | 0.09 | 9.96 | 4.73 |
| **95th %** | 0.67 | 62.5 | 85.2 | 0.27 | 65.9 | 85.5 | 0.40 | 61.9 | 85.5 | 0.70 | 57.9 | 84.1 |
| **75th %** | 0.49 | 51.9 | 80.8 | 0.25 | 57.1 | 81.7 | 0.37 | 52.1 | 81.7 | 0.62 | 47.7 | 77.9 |
| **50th %** | 0.35 | 42.8 | 76.2 | 0.23 | 45.8 | 79.5 | 0.33 | 44.0 | 76.7 | 0.53 | 39.8 | 74.5 |
| **25th %** | 0.26 | 36.6 | 72.8 | 0.20 | 38.6 | 74.4 | 0.30 | 37.7 | 73.5 | 0.46 | 33.7 | 71.6 |
| **5th %** | 0.19 | 29.7 | 69.2 | 0.16 | 33.9 | 70.5 | 0.28 | 32.1 | 70.5 | 0.42 | 27.7 | 68.1 |
| **Interquartile range** | 0.23 | 15.3 | 8.04 | 0.05 | 18.5 | 7.34 | 0.06 | 14.3 | 8.17 | 0.16 | 14.0 | 6.26 |

NDVI: Normalised Difference Vegetation Index. Ox: Oxidant Capacity (Ox = [(1.07 x NO2) + (2.075 x O3)]/3.145). Greenness exposure is defined as 16-day average NDVI in the 500m buffer around patient’s residence address during follow-up. The NDVI were grouped into three tertiles with 692 patients in Tertile T1, 691 in T2 and 992 T3, respectively.

Table 3 Adjusted hazard ratios (95% confidence intervals) per 10µg/m3 increase in PM2.5 associated with mortality among MDR-TB patients stratified by treatment and type of drug resistance from single-pollutant and oxidant models in the full cohort (n = 2,305) and across the three tertiles of greenness (i.e. NDVI) within the 500m buffer around patient’s residence.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All cases** | **Treated**\* | **Untreated** | **Primary resistance**† | **Acquired resistance** |
| n=2305 | n=1,716 | n=589 | n=770 | n=1,535 |
| **Single-pollutant Model** |  |  |  |  |  |
| Full cohort | 1.581 (1.567, 1.595) | 1.660 (1.620, 1.700) | 1.498 (1.476, 1.521) | 1.453 (1.421, 1.486) | 1.638 (1.623, 1.654) |
| Tertile 1 | 2.226 (1.880, 2.635) | 2.407 (2.063, 2.807) | 2.097 (2.023, 2.173) | 1.989 (1.647, 2.402) | 2.283 (1.953, 2.667) |
| Tertile 2 | 2.085 (1.950, 2.229) | 2.210 (2.038, 2.397) | 2.312 (2.286, 2.337) | 2.132 (1.707, 2.663) | 2.082 (2.072, 2.092) |
| Tertile 3 | 2.025 (1.976, 2.075) | 2.461 (2.379, 2.545) | 1.684 (1.634, 1.736) | 1.915 (1.898, 1.932) | 2.082 (2.024, 2.142) |
| **Oxidants Model** |  |  |  |  |  |
| Full cohort | 1.702 (1.680, 1.725) | 1.828 (1.778, 1.879) | 1.590 (1.556, 1.623) | 1.590 (1.560, 1.620) | 1.740 (1.713, 1.768) |
| Tertile 1 | 2.478 (1.789, 3.433) | 2.903 (1.783, 4.725) | 2.383 (2.231, 2.546) | 2.140 (1.446, 3.169) | 2.550 (1.823, 3.566) |
| Tertile 2 | 2.872 (2.660, 3.101) | 3.694 (3.027, 4.508) | 2.436 (2.418, 2.454) | 3.358 (2.504, 4.503) | 2.754 (2.590, 2.927) |
| Tertile 3 | 1.169 (1.162, 1.175) | 2.037 (1.961, 2.115) | 1.754 (1.747, 1.761) | 1.680 (1.564, 1.803) | 1.950 (1.927, 1.974) |

Hazard ratios are calculated per 10*µ*g/m3 increase in exposure; all Cox models presented in the table met the proportional hazard assumption according to Schoenfeld residuals. Cox models for all-cause mortality are adjusted for covariates: age, sex, ethnicity, type of drug resistance, treated or untreated, primary or acquired resistance, living province, working environment, place of residence (urban or rural), altitude, and NTL. Covariates excluded in the Cox models due to violation of the proportionality assumption: occupation. NDVI: Normalized Difference Vegetation Index. NTL: nighttime light index. Ox: Oxidant Capacity (Ox = [(1.07 x NO2) + (2.075 x O3)]/3.145).

\* Treated cases are defined as patients had or have taken 24-month standardized MDR-TB treatments; otherwise untreated.

† Cases without taking any TB-related treatment before MDR-TB diagnosis are suggested to obtain multi-drug resistance from infection of MDR-TB bacteria directly, named “primary resistance”; cases had TB-related treatment before MDR-TB diagnosis are suggested to obtain multi-drug resistance by acquiring from Mtb. bacteria mutations, named” acquired resistance.”

Table 4. Adjusted hazard ratios (HRs) for annual mean PM2.5 and mortality among MDR-TB patients stratified by age, sex, place of residence, and province for the full cohort and across the three tertiles of NDVI within 500m buffer around patient’s residence, after adjusting for Ox in oxidant-pollutant models.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Full cohort (range 0.008 to 0.850)** | **Tertile 1 (range 0.008 to 0.275)** | **Tertile 2 (range 0.276 to 0.408)** | **Tertile 3 (range 0.409 to 0.850)** |
|  | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| **By Age (years old)**  *<* 60 | 2.434 (2.432, 2.435) | 3.093 (2.639, 3.626) | 4.431 (4.117, 4.770) | 3.462 (3.430, 3.495) |
| ≥ 60 | 1.487 (1.475, 1.501) | 2.383 (1.619, 3.508) | 1.756 (1.368, 2.253) | 1.443 (1.326, 1.571) |
| **By Sex**  Male | 1.644 (1.611, 1.678) | 2.226 (1.721, 2.879) | 2.083 (1.422, 3.052) | 2.013 (1.611, 2.772) |
| Female | 2.209 (1.874, 2.845) | 2.387 (2.269, 3.181) | 2.401 (2.092, 3.217) | 2.125 (2.178, 3.231) |
| **By Place of Region**  Urban area | 1.739 (1.631, 1.854) | 3.152 (2.149, 4.625) | 3.149 (3.013, 3.291) | 1.950 (1.235, 3.079) |
| Rural area  **By Province**  Zhejiang  Ningxia | 1.780 (1.731, 1.829)  1.059 (1.049, 1.069)  1.221 (1.078, 1.385) | 2.490 (1.749, 3.546)  1.074 (1.053, 1.095)  1.222 (1.039, 1.437) | 2.796 (2.682, 2.915)  1.069 (1.046, 1.096)  1.535 (0.930, 2.531) | 2.164 (2.035, 2.302)  1.052 (1.035, 1.070)  --- |

Hazard ratios (95% confidence intervals) are calculated per 10µg/m3 increase in exposure; all Cox models presented in the table met the proportional hazard assumption according to Schoenfeld residuals. Cox models for all-cause mortality are adjusted for covariates: age, sex, ethnicity, type of drug resistance, treated or untreated, primary, or acquired resistance, province, working environment, place of residence (urban or rural), altitude, NTL. Covariates excluded in the Cox models due to violation of the proportionality assumption: occupation. NDVI: Normalised Difference Index. NTL: nighttime light index. Ox: Oxidant Capacity (Ox = [(1.07 x NO2) + (2.075 x O3)]/3.145).