Original research

Effect modification of greenness on $PM_{2.5}$ associated all-cause mortality in a multidrug-resistant tuberculosis cohort

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ABSTRACT

Rationale Evidence for the association between fine particulate matter ($PM_{2.5}$) and mortality among patients with tuberculosis (TB) is limited. Whether greenness protects air pollution-related mortality among patients with multidrug-resistant tuberculosis (MDR-TB) is completely unknown.

Methods 2305 patients reported in Zhejiang and Ningxia were followed up from MDR-TB diagnosis until death, loss to follow-up or end of the study (31 December 2019), with an average follow-up of 1724 days per patient. 16-day averages of contemporaneous Normalised Difference Vegetation Index (NDVI) in the 500 m buffer of patient's residence, annual average $PM_{2.5}$ and estimated oxidant capacity O_x were assigned to patients regarding their geocoded home addresses. Cox proportional hazards regression models were used to estimate HRs per 10 $\mu g/m^3$ exposure to $PM_{2.5}$ and all-cause mortality among the cohort and individuals across the three tertiles, adjusting for potential covariates.

Results HRs of 1.702 (95% CI 1.680 to 1.725) and 1.169 (1.162 to 1.175) were observed for $PM_{2.5}$ associated with mortality for the full cohort and individuals with the greatest tertile of NDVI. Exposures to $PM_{2.5}$ were stronger in association with mortality for younger patients (HR 2.434 (2.432 to 2.435)), female (2.209 (1.874 to 2.845)), patients in rural (1.780 (1.731 to 1.829)) and from Ningxia (1.221 (1.078 to 1.385)). Cumulative exposures increased the HRs of $PM_{2.5}$-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 $PM_{2.5}$ and mortality. Improving greener space and air quality may contribute to lower the risk of mortality from TB/MDR-TB and other diseases.

Key messages

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 $PM_{2.5}$ impairs important components of the protective human lung and results in suppressing systemic immune response against *Mycobacterium tuberculosis*, whereas this impact of air pollution may be overstated if greenness was not considered.

Why read on?

- Consistent with the experimental evidence of oxidative stress and inflammatory effects of $PM_{2.5}$, our study, the largest MDR-TB cohort, shows that exposure to ambient $PM_{2.5}$ 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 $PM_{2.5}$.

INTRODUCTION

Earlier studies have shown that particular matter (PM) in alveolar macrophages alters *Mycobacterium 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 patients with TB.[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 $PM_{2.5}$ 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

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drugs. One previous study in 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 psychological 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 $PM_{2.5}$ 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 m around patient's residence during 11 years of follow-up (2009–2019), respectively. Oxidant capacity (O_x) is incorporated in our models as previous studies showed that they were associated with more chronic health outcomes, like TB, than either O_3 or NO_2 alone.[13 14]

We hypothesise that living in greener areas attenuated the risk of $PM_{2.5}$-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 susceptibility 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 1 January first 2009 to 31 December 2017 were eligible for inclusion. We enrolled all confirmed cases diagnosed between 1 January 2009 and 31 December 2017 in Zhejiang and between 1 January 2015 and 31 December 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

Patients with MDR-TB 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 31 December 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 $PM_{2.5}$ was from the space-time extremely randomised 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 satellites.[16 17] The annual $PM_{2.5}$ were synthesised from the daily $PM_{2.5}$ 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]

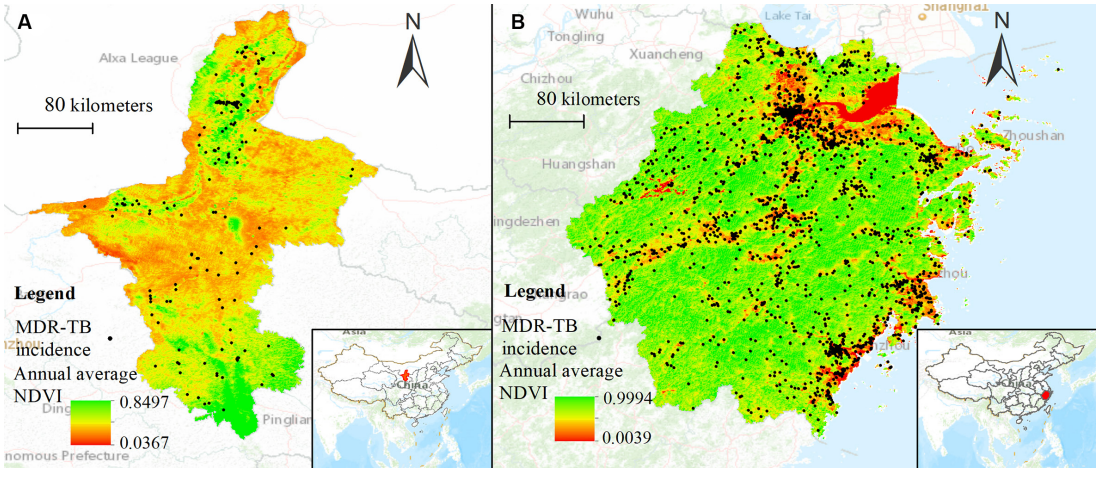

Figure 1 Characteristics of multidrug-resistant tuberculosis (MDR-TB) distribution and greenness (ie, Normalised Difference Vegetation Index (NDVI)) in (A) Ningxia and (B) Zhejiang, China.

Table 1 Characteristics of individuals at baseline in the full cohort (n=2305) and across tertiles of greenness (ie, NDVI) within 500 m buffer around patient's residence

	Greenness tertile*			
	Full cohort (range 0.008–0.850)	Tertile 1 (range 0.008–0.275)	Tertile 2 (range 0.276–0.408)	Tertile 3 (range 0.409–0.850)
	n (%)	n (%)	n (%)	n (%)
All patients	2305 (100)	692 (30.0)	691 (29.9)	922 (40.0)
Stratified by sex				
Male	1674 (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	1664 (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	2243 (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	2268 (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	1716 (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	1535 (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	1729 (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	1548 (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	1710 (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)	1868 (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	2095 (90.9)	569 (24.7)	608 (26.4)	918 (39.8)
Nighttime Light (NTL)‡				
High NTL	1152 (50.0)	596 (25.9)	458 (19.9)	98 (4.25)
Low NTL	1153 (50.0)	96 (4.16)	233 (10.1)	824 (3.57)

*Greenness exposure is defined as 16-day average NDVI within 500 m buffer around patient's residence address during follow-up, dividing into tertiles.
†Altitude as proxy for meteorological factors, using the mean value of 200 m as the low-high cut-off.
‡NTL: Nighttime Light Index as proxy for socioeconomic and urbanisation level, using the median value of 6.42 as the low-high cut-off.
MDR, multidrug resistant; NDVI, Normalised Difference Vegetation Index; XDR, extensively drug resistant.

The estimated annual mean $PM_{2.5}$ were highly consistent with the ground-based measurements with a high correlation coefficient (R^2=0.94) in China.[17] Additionally, we calculated the combined oxidant capacity (O_x) of O_3 and NO_2 as a weighted average with weights equivalent to their respective redox potentials (ie, $O_x=[(1.07\times NO_2) + (2.075\times O_3)]/3.145$).[18] Daily NO_2 and O_3 were obtained from the National Air Quality Network of the Chinese Ministry of Environmental Protection. The annual concentrations of NO_2 were derived from a temporally adjusted national land-use regression model that combined 1500 fixed-site nationwide monitoring data, satellite NO_2 estimates, road length within 10 km, industrial land-use areas within various buffers and meteorological factors.[19] Ozone exposures were estimated based on 8-hour average daily maximum concentrations by integrating monitoring O_3 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, NO_2 and O_3 were not included to reduce multilinearities with $PM_{2.5}$ and O_x.

Greenness

The Normalised 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] Sixteen-day average greenness surface data at 500 m×500 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 previous study[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.

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 (ie, 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 (ie, Zhejiang or Ningxia), place of residence (ie, urban or rural), altitude as a proxy for meteorological factors, like temperature, monthly average Nighttime Light Index (NTL) as a proxy for socioeconomic and urbanisation 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 and higher urbanisation level. The altitude and monthly NTL were publicly available from the NASA's Socioeconomic Data and Applications Centre with details about NTL data can be found in previous study.[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 patients with MDR-TB were stratified by individual characteristics, treatment history and environment where they live across tertiles of NDVI. The association between $PM_{2.5}$ and mortality was assessed using the Cox proportional hazards regression model with O_x adjusted for the full cohort and the three tertiles, separately. HRs were calculated per 10 $\mu g/m^3$ and presented with 95% CIs. 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.

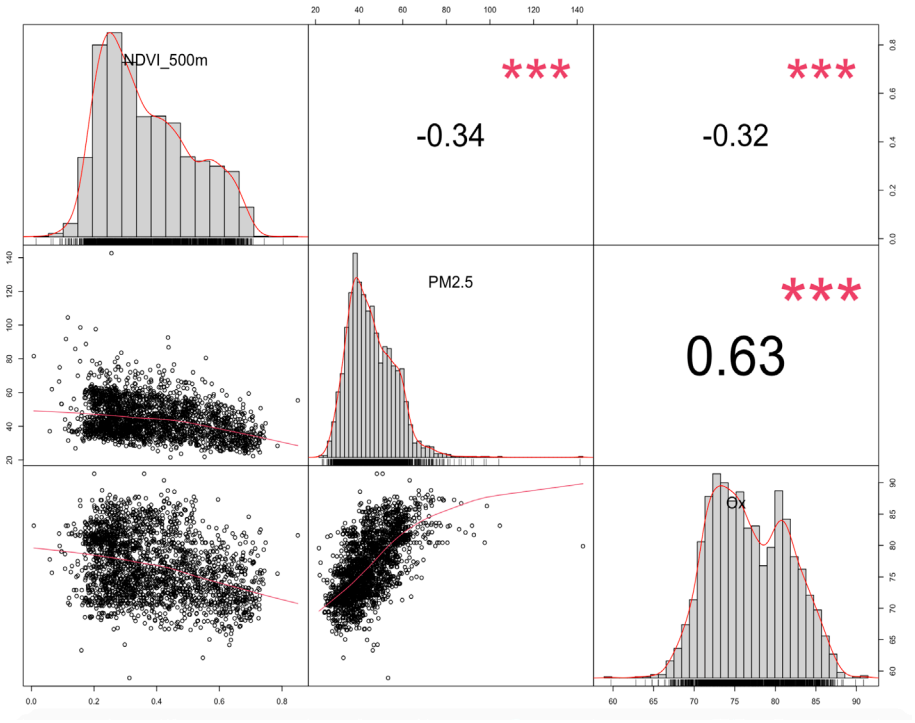

Figure 2 Correlations among exposures variables (NDVI, $PM_{2.5}$ and O_x) for the 2305 patients with complete covariates. NDVI, Normalised Difference Vegetation Index; O_x, oxidant capacity (O_x=[(1.07×NO_2)+(2.075×O_3)]/3.145); $PM_{2.5}$, fine particulate matter.

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 $PM_{2.5}$-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.

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 2305 MDR-TB cases with 2095 from Zhejiang and 210 from Ningxia in the study. All patients were reported between 2009 and 2017, and followed to 31 December 2019, with an average follow-up of 1724 days per patient. Among the patients, there were 525 deaths during the period of follow-up.

Descriptive statistics

Of 2305 cases, 1674 (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, 1535

Table 2 Baseline characteristics by NDVI, $PM_{2.5}$ (μg/m^3) and O_x (ppb) assigned to individuals in the full cohort (n=2305) and across the three tertiles of greenness (i.e., NDVI) within 500 m buffer around patient's residence

	Full cohort (range 0.008–0.850)			Tertile 1 (range 0.008–0.275)			Tertile 2 (range 0.276–0.408)			Tertile 3 (range 0.409–0.850)		
	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
SD	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
IQR	0.23	15.3	8.04	0.05	18.5	7.34	0.06	14.3	8.17	0.16	14.0	6.26

Greenness exposure is defined as 16-day average NDVI in the 500 m buffer around patient's residence address during follow-up. The NDVI were grouped into three tertiles with 692 patients in Tertile T1, 691 patients in T2 and 992 patients in T3, respectively.
NDVI, Normalised Difference Vegetation Index; O_x, oxidant capacity (O_x = [(1.07 x NO_2) + (2.075 x O_3)]/3.145).;

Table 3 Adjusted HRs (95% CIs) per 10 μg/m^3 increase in $PM_{2.5}$ associated with mortality among patients with MDR-TB stratified by treatment and type of drug resistance from single-pollutant and oxidant models in the full cohort (n=2305) and across the three tertiles of greenness (ie, NDVI) within the 500 m buffer around patient's residence

	All cases	Treated*	Untreated	Primary resistance†	Acquired resistance
	n=2305	n=1716	n=589	n=770	n=1535
Single-pollutant model					
Full cohort	1.581 (1.567 to 1.595)	1.660 (1.620 to 1.700)	1.498 (1.476 to 1.521)	1.453 (1.421 to 1.486)	1.638 (1.623 to 1.654)
Tertile 1	2.226 (1.880 to 2.635)	2.407 (2.063 to 2.807)	2.097 (2.023 to 2.173)	1.989 (1.647 to 2.402)	2.283 (1.953 to 2.667)
Tertile 2	2.085 (1.950 to 2.229)	2.210 (2.038 to 2.397)	2.312 (2.286 to 2.337)	2.132 (1.707 to 2.663)	2.082 (2.072 to 2.092)
Tertile 3	2.025 (1.976 to 2.075)	2.461 (2.379 to 2.545)	1.684 (1.634 to 1.736)	1.915 (1.898 to 1.932)	2.082 (2.024 to 2.142)
Oxidants model					
Full cohort	1.702 (1.680 to 1.725)	1.828 (1.778 to 1.879)	1.590 (1.556 to 1.623)	1.590 (1.560 to 1.620)	1.740 (1.713 to 1.768)
Tertile 1	2.478 (1.789 to 3.433)	2.903 (1.783 to 4.725)	2.383 (2.231 to 2.546)	2.140 (1.446 to 3.169)	2.550 (1.823 to 3.566)
Tertile 2	2.872 (2.660 to 3.101)	3.694 (3.027 to 4.508)	2.436 (2.418 to 2.454)	3.358 (2.504 to 4.503)	2.754 (2.590 to 2.927)
Tertile 3	1.169 (1.162 to 1.175)	2.037 (1.961 to 2.115)	1.754 (1.747 to 1.761)	1.680 (1.564 to 1.803)	1.950 (1.927 to 1.974)

HRs are calculated per 10 μg/m^3 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.
*Treated cases are defined as patients had or have taken 24-month standardised MDR-TB treatments; otherwise untreated.
†Cases without taking any TB-related treatment before MDR-TB diagnosis are suggested to obtain multidrug resistance from infection of MDR-TB bacteria directly, named 'primary resistance'; cases had TB-related treatment before MDR-TB diagnosis are suggested to obtain multidrug resistance by acquiring from Mtb. bacteria mutations, named 'acquired resistance'.
NDVI, Normalised Difference Vegetation Index; NTL, Nighttime Light Index; O_x, oxidant capacity (O_x=[(1.07xNO_2)+(2.075xO_3)]/3.145).;

(66.6%) had no received any TB treatment indicating primary resistance, while 770 (33.4%) were treated indicating acquired resistance. Of all patients, 1716 (74.4%) received MDR-TB treatment, while 589 (25.6%) did not take the treatment (table 1). A higher proportion of patients with MDR-TB lived in rural (74.2%), low altitude (≤200 m, 81%) areas. Approximately 20% patients worked indoors, while 12% were engaged in intelligent-intensive work.

Mean levels of exposures

Table 2 shows the mean distribution of NDVI, $PM_{2.5}$ and O_x associated with individuals in the full cohort and across the three tertiles of greenness (NDVI, T1: 0.008–0.275, T2: 0.276–0.408, T3: 0.409–0.850) within 500 m 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 $PM_{2.5}$ and O_x declines ($PM_{2.5}$, T1: 48.4 μg/m^3, T2: 45.4 μg/m^3, T3: 41.2 μg/m^3; O_x, T1: 78.3 μg/m^3, T2: 77.4 μg/m^3, T3: 75.1 μg/m^3). NDVI is moderately negatively associated with $PM_{2.5}$ (ρ=−0.34) and O_x (ρ=−0.32), while the correlation between $PM_{2.5}$ and O_x is positive and relatively stronger (ρ=0.63) during the follow-up (figure 2).

Table 4 Adjusted HRs for annual mean $PM_{2.5}$ and mortality among patients with MDR-TB stratified by age, sex, place of residence, and Province for the full cohort and across the three tertiles of NDVI within 500 m buffer around patient's residence, after adjusting for O_x in oxidant-pollutant models

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

HRs (95% CIs) are calculated per 10 μg/m^3 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; O_x, oxidant capacity (O_x=[(1.07xNO_2) + (2.075xO_3)]/3.145).;

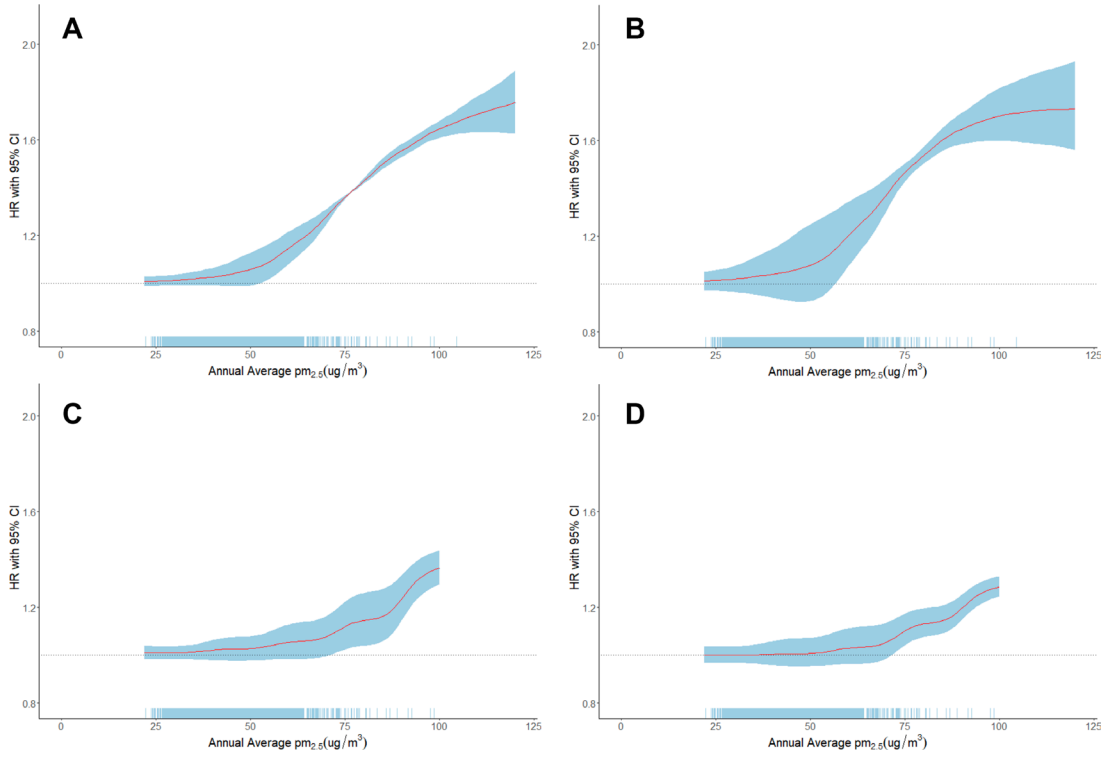

Figure 3 Association curves (in red) with 95% CIs (in light blue) for annual mean $PM_{2.5}$ and mortality for (A) the full cohort of 2305 patients with MDR-TB and individuals under different tertiles of contemporaneous NDVI, (B) Tertile 1 of contemporaneous NDVI, (C) Tertile 2 of contemporaneous NDVI, (D) Tertile 3 of contemporaneous NDVI. Through the analysis of variance test and the calculation of the Tukey's Honest Significant Differences, we found that the HRs of tertials 2 and 3 were 0.194 (95% CI 0.129 to 0.259) and 0.188 (95% CI 0.123 to 0.253) lower than that of tertile 1 on average, respectively. NDVI, Normalised Difference Vegetation Index; $PM_{2.5}$, fine particulate matter.

HRs from Cox regression models

Table 3 shows the results of single-pollutant 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 $PM_{2.5}$ was significantly associated with mortality in both single-pollutant (HR 1.581, 95% CI 1.567 to 1.595 per 10 $\mu g/m^3$ increase in $PM_{2.5}$) and oxidant-pollutant models (HR 1.702, 95% CI 1.680 to 1.725) for the full cohort. The effect modifications by greenness were slightly stronger for untreated (HR 1.498, 95% CI 1.476 to 1.521) than treated patients (HR 1.660, 95% CI 1.620 to 1.700), and for those who obtained MDR-TB through primary resistance (HR 1.453, 95% CI 1.421 to 1.486) than through acquired resistance (HR 1.638, 95% CI 1.623 to 1.654) in single-pollutant models. Similar associations were observed adjusting for O_x in oxidant-pollutant models. Consistent with previous studies,[10] we did not find a monotonic trend in the effect of $PM_{2.5}$ 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.

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 shows the stratified analysis results, suggesting that exposure to $PM_{2.5}$ were stronger in association with mortality for younger patients (HR 2.434, 95% CI 2.432 to 2.435 (<60 years) vs HR 1.487, 95% CI 1.475 to 1.501 (≥60 years)), female (HR 2.209, 95% CI 1.874 to 2.845 (female) vs HR 1.644, 95% CI 1.611 to 1.678 (male)) and patients from Ningxia province (HR 1.221, 95% CI 1.078 to 1.385 (Ningxia) vs HR 1.059, 95% CI 1.049 to 1.069 (Zhejiang)). For patients living in rural, the HR was 1.780 (95% CI 1.731 to 1.829) slightly higher than those living in urban areas (HR 1.739, 95% CI 1.631 to 1.854). Exposure to $PM_{2.5}$ 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 $PM_{2.5}$ exposure and mortality among patients with MDR-TB for the full cohort (figure 3A) and the three tertiles (figure 3B–D) of NDVI, within the 500 m buffer around patient's residence. Cumulative exposures increased the HRs of $PM_{2.5}$-related mortality, while greater greenness substantially flattened the risk with the HRs reduced in 0.188 (95% CI 0.123 to 0.253) (tertile 2, figure 3C) to 0.194 (95% CI 0.129 to 0.259) (tertile 3, figure 3D) on average, compared with the lowest greenness (tertile 1, figure 3B).

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 $PM_{2.5}$ on

mortality among patients with TB is still sparse. Furthermore, fewer have examined for MDR-TB and how greenness modifies the risk of $PM_{2.5}$-related mortality. Our study found a 70.2% increase in mortality per 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure, after adjusting for O_x, in the full MDR-TB cohort. Greater exposure to greenness lowered the impacts of $PM_{2.5}$ for untreated and primary resistance patient groups, except those taking MDR-TB treatment. Our data suggested that living in lower greenery neighbourhoods increased risks of mortality associated with $PM_{2.5}$, particularly in elderly (≥60 years), male and patients from urban areas, while it did not show that greenness attenuated the effect of $PM_{2.5}$ 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 2305 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 $PM_{2.5}$ and mortality were consistent for both the full cohort and the three different greenness levels as well.

The adverse effects of ambient $PM_{2.5}$ 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 patients with MDR-TB. A Chinese cohort found that exposure to $PM_{2.5}$ 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 $PM_{2.5}$ and all-cause mortality for the full cohort of patients with MDR-TB was higher, suggesting that patient with MDR-TBs 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 $PM_{2.5}$ exposure in the 500 m radium around participant's residence. Although no studies have examined the effect modification by greenness among patients with TB or MDR-TB, Ji *et al*'s estimates of greenness in reducing risks of all-cause mortality relevant to $PM_{2.5}$ 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 $PM_{2.5}$ exposure and non-accidental mortality during 11 years of follow-up. They found that individuals in deprived neighbourhoods with high greenness benefitted by having more attenuated associations between $PM_{2.5}$ 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 $PM_{2.5}$ associated with mortality.[10 37] However, the literature has been inconsistent. Our observed more attenuated risks of mortality relevant to $PM_{2.5}$ 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 patients with MDR-TB in Zhejiang and Ningxia, two provinces implemented rigorous diagnosis methods and 24-month standardised 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 (overestimation or underestimation) and selection, although low, might still be possible. Although we have adjusted for a set of potential individual and contextual covariates, which minimised but might not have entirely eliminated confounding. For example, some patients with MDR-TB received individual adjusted treatment when standardised 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 HR of $PM_{2.5}$ could not be confirmed for only four cases in the most greenery areas (ie, the third tertile of NDVI) of Ningxia given its relatively small population. Different vegetation types might have different abilities in absorbing air pollutants.[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 $PM_{2.5}$ and mortality among patients with MDR-TB. Improving green space and air quality, along with effective treatments, may contribute to the reduction of mortality for MDR-TB.

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