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碩士論文

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空氣污染與結核病風險之世代研究

Ambient air pollution and risk of active tuberculosis: a nationwide population-based cohort study in Taiwan

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摘要

背景

目前關於長期暴露於直徑小於或等於2.5微米的懸浮微粒（$PM_{2.5}$）與結核病之間關係的證據有限且不一致。本研究旨在利用來自臺灣全國代表性樣本來調查兩者間的關聯性。

方法

我們對參加了2001年至2017年間五次全國健康訪問調查的12歲及以上個體進行了一項長期追蹤研究。每位參與者在發生結核病、死亡或2020年12月31日之前均進行了隨訪。個體基於ICD代碼和抗結核藥物處方被診斷為發生結核病。$PM_{2.5}$暴露是使用空氣質量監測站和微型傳感器數據估計的。我們進行了時間相依的Cox迴歸分析，使用前兩年的平均$PM_{2.5}$水平作為暴露窗口。受限制的立方曲線被用來檢驗非線性關聯。

結果

在追蹤時間中位數為11年的72180名個體中，報告了488例結核病病例。隨訪的第一年，平均$PM_{2.5}$水平為31.0 μg/m^3（標準差: 9.7 μg/m^3）。調整性別、年齡、身體質量指數、吸菸、飲酒、教育程度、家庭平均月收入、居住在山地行政區、結核病病史和結核病的時間趨勢後，$PM_{2.5}$年平均值每增加10 μg/m^3 調整後的HR為0.94（CI: 0.84-1.05）。受限制的立方曲線Cox迴歸分析的結果顯示，$PM_{2.5}$和結核病之間可能存在非線性關係（*p*-value for non-linearity: 0.084）。我們還觀察到年齡的

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效應修飾（*p*-value: 0.048），在65歲以上和65歲以下的個體之間結核病風險存在顯著差異。改變暴露窗口和結點選擇方法對主要結果影響有限。

結論

這項大型基於人口的世代研究結果顯示，$PM_{2.5}$和結核病之間可能存在非線性關係，特別是在低濃度下呈現反向關係。老年族群可能是受空氣污染影響的易感族群。

關鍵字

懸浮微粒，$PM_{2.5}$，結核病，時間相依Cox迴歸，非線性擬合

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Abstract

Background

Available evidence on the relationship between long-term exposure to particulate matter with aerodynamic diameter of ≤ 2.5 μm ($PM_{2.5}$) and tuberculosis (TB) has been limited and inconsistent. This study aimed to investigate this association using a nationally representative sample from Taiwan.

Methods

We conducted a longitudinal cohort study on individuals aged ≥12 years who participated in 5 rounds of the National Health Interview Survey from 2001 to 2017. Participants were followed up until the incidence of active TB, death, or 31 December 2020. TB incidence was identified based on ICD codes and prescription of anti-TB drugs. $PM_{2.5}$ exposure was estimated using air quality monitoring stations and microsensors data. Time-dependent Cox regression analyses were conducted, using the average $PM_{2.5}$ level in the preceding two years as the exposure window. Nonlinear associations were examined using restricted cubic splines.

Results

Among 72,180 individuals with a median follow-up time of 11 years, 488 TB cases were reported. During the first year of follow-up, the mean $PM_{2.5}$ level was 31.0 μg/m^3 (SD: 9.7 μg/m^3). After adjusting for sex, age, body mass index, cigarettes smoking, alcohol use, education level, household income, living in mountain administrative areas, TB history, and secular trend of TB, the adjusted HR was 0.94 (CI: 0.84-1.05) for every 10 μg/m^3 increase with preceding two years average $PM_{2.5}$ level. The results of the

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restricted cubic spline Cox regression analysis suggested a potential nonlinear relationship between $PM_{2.5}$ and TB (*p*-value for non-linearity: 0.084). We also observed effect modification by age (*p*-value: 0.048), with a significant difference in TB risk between individuals aged above 65 years and those aged 65 years and below. Changing the exposure window and knot selection method had limited impact on the main findings.

Conclusions

In the large population-based cohort study, the results revealed a nonlinear relationship between $PM_{2.5}$ and TB, particularly an inverse relationship at low levels. The elderly population might be the vulnerable subgroup for the effect of air pollution.

Key word

particulate matter, $PM_{2.5,}$ tuberculosis, time-dependent Cox regression, restricted cubic splines

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Chapter 1 Introduction

Air pollution is recognized by the World Health Organization (WHO) and the European Environment Agency as the greatest environmental health risk and is associated with stroke, heart disease, lung cancer, acute and chronic respiratory diseases.[1,2] The particulate matter with aerodynamic diameter of ≤ 2.5 μm ($PM_{2.5}$) is referred to as fine particles and is primarily derived from combustion emissions (e.g. gasoline, diesel, wood) and industrial processes.[3] As of today, the threshold value for $PM_{2.5}$, which is not harmful to human health, has not been identified. In WHO global air quality guidelines, the recommended standard for $PM_{2.5}$ is an annual average of 5 $\mu g/m^3$ (long-term).[4] However, in 2019, 99% of the world's population lived in areas that exceeded the WHO $PM_{2.5}$ recommended standard.[1] The Health Effects Institute and the Institute for Health Metrics and Evaluation's Global Burden of Disease project estimated that long-term exposure to $PM_{2.5}$ contributed to 4.14 million deaths worldwide in 2019.[5]

Tuberculosis (TB) is caused by Mycobacterium tuberculosis and primarily spreads through aerosols dispersed in the air by TB-infected people (e.g. coughing). If the lung immune system is unable to defend itself against Mycobacterium tuberculosis in time, the host may become infected. Tobacco smoke was reported to be associated with TB and has been recognized as a risk factor for TB by the WHO.[6,7,8] Previous studies suggest that tobacco smoke disrupts the lung immune system leading to increased susceptibility to Mycobacterium tuberculosis.[9,10,11,12] However, the relationship between $PM_{2.5}$, which is also a particulate matter, and TB has not been established. Available evidence on the relationship between the long-term effects of $PM_{2.5}$ (at least one year of exposure or lag effect) and TB was limited. (Appendix Table S1)

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To date, only three epidemiological studies with individual-level information have reported the risk of $PM_{2.5}$ and TB. Smith et al. (2016) conducted a nested case-control study in northern California, USA, the participants were selected from the members of Kaiser Permanente Northern California.[13] They identified 2,309 cases of newly diagnosed TB between 1996 and 2010. The cases were matched with 4,604 controls based on age, sex, and race/ethnicity. The definition of TB included either an initial positive TB culture or a new clinical diagnosis accompanied by a minimum of 30 days of anti-TB medication. Each participant's exposure data were obtained as the average concentration from the closest monitoring station average throughout the 24 months prior to study entry. The range of exposure varied from 0.1 to 26.5 $\mu g/m^3$, with a median of 9.6 $\mu g/m^3$ (20th percentile: 8.6 $\mu g/m^3$, 80th percentile: 11.7 $\mu g/m^3$). Compared to the reference group (1st quintile), the adjusted odds ratios were as follows: 1.13 (95% confidence interval, CI: 0.90-1.41) for the 2nd quintile, 1.09 (CI: 0.87-1.37) for the 3rd quintile, 1.11 (CI: 0.87-1.42) for the 4th quintile, and 0.94 (CI: 0.73-1.23) for the 5th quintile. No significant dose response relationships was observed.

Wu et al. conducted a propensity-matched cohort study in Kaohsiung, Taiwan, utilizing the Kaohsiung Medical University Hospital Research Database as the source of personal information.[14] In this study, participants diagnosed with pneumonia were selected as the reference group for propensity matching. Subsequently, participants were matched based on factors including age, sex, and comorbidities associated with TB. The definitions of pneumonia, TB, and comorbidities associated with TB were established using the ICD-9-CM codes in the participants' medical records. The exposure data for each participant were obtained by calculating the average concentration from the closest

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monitoring station throughout the follow-up period. The study cohort comprised a total of 82,590 participants (16,518 with pneumonia) with a median follow-up of 3.5 years. The range of exposure varied from 4.3 to 72.3 μg/m^3, with a median of 30.5 μg/m^3 (Q1: 29.5 μg/m^3, Q3: 30.8 μg/m^3, interquartile range, IQR: 1.3 μg/m^3) and a mean of 30.4 μg/m^3 (standard deviation, SD: 3.7 μg/m^3). During a seven-year follow-up period from 2012 to 2018, a total of 1,312 cases of TB were identified (395 cases in pneumonia group). Wu et al. observed a significant positive correlation between $PM_{2.5}$ and TB (adjusted HR: 1.13, CI: 1.12-1.15, for every 1 μg/m^3 increase).

Lai et al. conducted a cohort study in New Taipei City, Taiwan, utilizing data from the voluntary community-based integrated screening program conducted between 2005 and 2008.[15] The study participants were followed up until the identification of TB or December 2012. Through linking with the National TB Registry of Taiwan Centers for Disease Control using individuals' unique identification numbers, the status of TB for each participant has been obtained. According to the standards of the Taiwan Centers for Disease Control, the identification of TB requires undergoing physical examination, chest radiograph, sputum culture, sputum smear, or nucleic acid amplification tests. Lai et al. utilized time-varying $PM_{2.5}$ as the exposure. The exposure for each individual was updated annually, calculating the average concentration from the monitoring station closest to their residential address over the past two years. The cohort included 106,678 participants with a median follow-up of 6.7 years. The range of exposure varied from 19.1 to 35.1 μg/m^3, with a median of 27.8 μg/m^3 (Q1: 25.1 μg/m^3, Q3: 30.3 μg/m^3, IQR: 5.2 μg/m^3) and a mean of 27.5 μg/m^3 (standard deviation, SD: 3.4 μg/m^3). A total of 418 cases of newly diagnosed TB occurred between 2005 and 2012. In the multivariable

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analysis, Lai et al. estimated the adjusted hazard ratio (HR) of 1.39 (CI: 0.95-2.03) for every 10 μg/m^3 increase, using the Cox proportional hazards model.

Prior to this study, previous evidence suggested a link between long-term exposure to $PM_{2.5}$ and increased susceptibility to TB. In vitro cell experiments supported this notion by demonstrating that $PM_{2.5}$ can enhance TB susceptibility.[16] However, epidemiological studies did not consistently observe the same results. Moreover, the limited variability in exposure levels has posed challenges in drawing definitive conclusions in epidemiology. The potential misclassification of exposure and the narrow range of exposure variation have resulted in high uncertainty surrounding the estimated effects.

In Taiwan, there are a total of 86 air quality monitoring stations, which are unevenly distributed across an area of approximately 36,000 square kilometers. Previous studies utilized the average $PM_{2.5}$ concentration from the monitoring station that is closest to the residential address as a proxy for exposure. However, it is important to acknowledge that this approach may introduce some degree of misclassification. Additionally, when conducting long-term follow-up studies, it is necessary to consider the residential address changes that occur over time.[15] In Taiwan, approximately 600,000 individuals change their residential address at the township level annually.[17]

We conducted a longitudinal cohort study with a nationally representative sample serving as the study population. By utilizing a higher resolution measure of exposure and accounting for changes in individual residential addresses during the follow-up period, we aimed to provide evidence for the relationship between $PM_{2.5}$ and TB.

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Chapter 2 Method

2.1 Settings and study population

We conducted a prospective cohort study to investigate the relationship between $PM_{2.5}$ and TB. This cohort consisted of participants aged ≥12 years from 5 rounds of the National Health Interview Survey (NHIS) conducted in 2001, 2005, 2009, 2013, and 2017. NHIS provides baseline information about the participants at the time of the interview, including health status, health behaviors, medical utilization, demographics, and socioeconomic characteristics. By linking the NHIS database to the National Health Insurance Research Database (NHIRD) using the individual's unique national identification number, we were able to access each individual's date of TB incidence and death, TB history status, and address for each year. For each individual, we started follow-up on 1 January of the year after the sampling year. If the participant enrolled in more than two rounds of NHIS, the earliest response was used. Participants with incomplete data were not included in the analysis. Each participant was followed up until the incidence of TB, death, or 31 December 2020.

2.2 Measurement of $PM_{2.5}$

We used the methodology developed in previous studies, an prediction model including ground level measurements from 76 air quality monitoring stations and 1822 microsensors, to estimate the township level time varying $PM_{2.5}$ exposure in the main island of Taiwan from 2000 to 2020.[18,19] This model estimated $PM_{2.5}$ concentrations for all 3km × 3km grids on the main island of Taiwan utilising microsensors data and the robust kriging method, considering meteorological factors, traffic density, land use,

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point emissions, area-source emissions, population, and elevation. Data from air quality monitoring stations were used to validate the model performance. In 2017, for the annual average, the model performance was cross-validation R^2 (CV-R^2) = 0.79 and cross-validation root mean squared prediction error (CV-RMSPE) = 2.3 μg/m^3. The data for 2000 to 2016 were backward predicted using the correlation of average exposure over two consecutive years, and the model performance was CV-R^2 = 0.93 and CV-RMSPE = 2.3 μg/m^3.[18] Using the population-weighted average methodology, we converted the annual average $PM_{2.5}$ concentration data from 3km × 3km grids to township level. In this study, we also considered the change in address of the participants from year to year. Participants' addresses were estimated based on their household registration and the address of their most visited medical clinic, which has been used in previous studies.[19,20]

2.3 Measurement of TB status

Overall, the TB incidence in Taiwan is decreasing year by year. The incidence rate per 100,000 population had declined from 74.6 in 2002 to 33.2 in 2020.[21] (Appendix Figure S2) Between 1 January 2001 and 31 December 2020, participants were classified as incident TB cases with either: a) diagnosed with TB in the outpatient or emergency department of NHI hospital (ICD-9-CM: 010-018 before 2016, ICD-10: A15-A19 since 2016), taking two or more anti-TB drugs concurrently, and cumulative duration ≥ 28 days; b) cumulated hospitalized days in NHI hospitals for TB (ICD-9-CM: 010-018 before 2016, ICD-10: A15-A19 since 2016) ≥ 28 days. The date of first visit were considered to be the date of incidence. In accordance with Taiwan Guidelines for TB Diagnosis & Treatment, the diagnosis of TB was carefully evaluated by physicians

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based on chest radiograph, sputum culture, sputum smear, nucleic acid amplification tests.[22] To ensure the accuracy of the diagnosis, outpatient and emergency prescription drugs were also included in the assessment (at least two or more anti-TB drugs, See Appendix 2.4). Chen et al. validated this approach against the reference data from the National TB Registry, the sensitivity and specificity of NHI-based definition of TB in 2005 NHIS were 87.9% and 99.9%, respectively.[23]

2.4 Measurement of covariates

We included the following potential risk factors of TB as covariates in our multivariable analysis: sex (male and female); age (year), body mass index (underweight <18.5 kg/m^2, normal ≥18.5 kg/m^2 and <25 kg/m^2, overweight ≥25 kg/m^2 and <30 kg/m^2, and obese ≥30 kg/m^2), cigarettes smoking status (never, former, and current), alcohol use (never, moderate, and excessive), education level (junior high school or below, high school, and college and above), average monthly household income (<$30,000 New Taiwan Dollars (NTD), ≥$30,000 NTD and <$100,000 NTD, and ≥$100,000 NTD), living in mountain administrative areas (yes and no), TB history (yes and no), and calendar year.[24,25,26,27,28,29] Covariates were measured at baseline with the exception of the calendar year, which varied over time.

2.5 Statistical analysis

To estimate the HRs and 95% confidence intervals (CIs) for the association between $PM_{2.5}$ and active TB, we conducted time-dependent Cox hazards regression analyses, adjusting for sex, age, body mass index, cigarettes smoking status, alcohol use, education level, average monthly household income, living in mountain administrative areas, TB history, and calendar year. We used follow-up as time scale and updated each

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individual's exposure with a one-year cycle.[30,31] Restricted cubic spline was employed to assess potential nonlinear associations, using exposure percentiles as the knots (5th, 27.5th, 50th, 72.5th, and 95th percentiles).[32] Additionally, we conducted stratified analyses to explore potential effect modifications by age, sex, body mass index, cigarette smoking status, living in mountain administrative areas, and NHIS year. To ensure the robustness of the findings, we repeated the analysis using average exposure over different durations and employed various knot selection methods for restricted cubic splines. The selected knot selection methods included dividing the exposure range into four equal intervals (equal 3), five equal intervals (equal 4), and six equal intervals (equal 5), as well as using the 5th, 50th, and 95th percentiles to create four intervals, the 5th, 35th, 65th, and 95th percentiles to create five intervals, and the 5th, 27.5th, 50th, 72.5th, and 95th percentiles to create six intervals. Participants who were included in analysis had informed consent at the time of the NHIS interview. This study was approved by the Institutional Review Board on Biomedical Science Research of Academia Sinica (AS-IRB02-107267). All analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC).

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Chapter 3 Results

3.1 Population characteristics

The study cohort included 72,180 individuals, living in 349 different towns (covered 349/349 non-outlying island towns in Taiwan), with a median follow-up time of 11 years. Compared with the lowest exposure group, the highest exposure group had lower BMI, lower alcohol consumption, and lower average monthly household income (Table 1).

The annual average concentration of $PM_{2.5}$ in Taiwan was decreasing over the past 2 decades. From 2000 to 2020, the annual average of $PM_{2.5}$ at the township level decreased from 34.69 μg/m³ (standard deviation, SD: 12.99 μg/m³) to 14.39 μg/m³ (SD: 4.13 μg/m³) (Appendix Figure S1). During the first year of follow-up among 72,180 individuals, the mean $PM_{2.5}$ level was 31.0 μg/m³ (SD: 9.7 μg/m³), with a median of 30.2 μg/m³ (Q1: 23.7 μg/m³, Q3: 37.5 μg/m³, interquartile range, IQR: 13.8 μg/m³) and a range of 48.3 μg/m³.

3.2 Incidence of TB and Cox hazard regression

During the follow-up period, a total of 488 TB cases were reported with an incidence rate of 62.7 per 100,000 population. The incidence rate of TB per 100,000 population was 93.3 in the first quartile, 51.9 in the second quartile, 44.5 in the third quartile, and 68.8 in the fourth quartile. In the Cox proportional hazards model adjusted for sex and age (Table 2, Model 1), the correlation between $PM_{2.5}$ and TB incidence was positive (adjusted HR: 1.10, CI: 1.00-1.22, for every 10 μg/m³ increase). After including additional confounding variables of sex, age, body mass index, cigarettes smoking

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status, alcohol use, education level, average monthly household income, living in mountain administrative areas, and TB history (Table 2, Model 2), a stronger positive correlation between $PM_{2.5}$ and the TB incidence was observed (adjusted HR: 1.18, CI: 1.07-1.31, for every 10 μg/m^3 increase). However, after additional adjustment for the calendar time trend to account for the simultaneous declining trend of air pollution and TB in Taiwan, $PM_{2.5}$ and TB risk was not significantly associated (adjusted HR: 0.94, CI: 0.84-1.05, for every 10 μg/m^3 increase) (Table 2, Model 3). In addition, people with current smoking (adjusted HR: 1.40, CI: 1.11-1.75) or excessive alcohol consumption (adjusted HR: 1.63, CI: 1.27-2.10) were at higher risk for developing active TB (Table 2, Model 3). In the nonlinear analysis using restricted cubic spline regression, we observed a U-shaped trend between $PM_{2.5}$ and TB risk. The risk of TB decreased with increasing $PM_{2.5}$ concentration before the $PM_{2.5}$ level of 25 μg/m^3, after which it began to increase. The *p*-value from the likelihood ratio test for non-linearity was 0.084 (Figure 2).

We repeated the analysis using different exposure windows and the results were similar to the main analysis. For every 10 μg/m^3 increase, the adjusted HR is 0.99 (CI: 0.89-1.10) for 1-year average, 0.99 (CI: 0.88-1.10) for 3-years average, 0.98 (CI: 0.87-1.10) for 4-years average, and 0.98 (CI: 0.87-1.10) for 5-years average. Under the different knot selection methods employed, consistent U-shaped trends were observed (Figure 3). The performance of different knot selection methods, including equal 3, equal 4, equal 5, percentile (5, 50, 95), percentile (5, 35, 65, 95), and percentile (5, 27.5, 50, 72.5, 95), was assessed based on the *p*-values obtained from the likelihood ratio test, which were 0.022, 0.049, 0.100, 0.022, 0.052, and 0.084, respectively.

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3.3 Stratified analysis

In the stratified analysis, we observed evidence of effect modification by age (*p*-value for effect modification: 0.048) (Table 3). For those above 65 years of age, the adjusted HR was 1.09 (CI: 0.91-1.31) with every 10 μg/m^3 increase in $PM_{2.5}$. The association was smaller for those aged below 65 (adjusted HR: 0.85, CI: 0.73-0.98). In terms of sex, body mass index, cigarettes smoking status, living in mountain administrative area, and NHIS year subgroups, no significant effect modification by $PM_{2.5}$ was observed.

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Chapter 4 Discussion

In this cohort study conducted in Taiwan, included 72,180 individuals, the linear Cox proportional hazards model did not show a significant association between $PM_{2.5}$ and TB (adjusted HR: 0.94, CI: 0.84-1.05 per 10 μg/m^3 increase), after adjusting for all of covariates. The results of the restricted cubic spline Cox regression analysis suggested a potential nonlinear relationship between $PM_{2.5}$ and TB. In stratified analysis, we observed effect modification by age, with a significant difference in TB risk between individuals aged above 65 years and those aged 65 years and below.

To date, research investigating the long-term effects of $PM_{2.5}$ on TB with individual-level information remains scarce. Although previous studies have reported harmful effects of $PM_{2.5}$ on TB, the narrow range of exposure levels and the potential measurement error of $PM_{2.5}$ led to greater uncertainty in the reported associations.

We addressed the limitations of previous studies by implementing the following improvements: Firstly, we utilized higher-resolution ground-level $PM_{2.5}$ exposure data instead of measurements provided by the closest monitoring station. Secondly, we took into account changes in residential addresses during the follow-up period. Thirdly, we accounted for the annual reduction of both $PM_{2.5}$ levels and TB incidence rates, eliminating the confounding effects of time trends. Lastly, we expanded our study sample to include a nationally representative cohort, ensuring a broader range of exposure. These improvements aimed to provide a more comprehensive and accurate understanding of the association between $PM_{2.5}$ and TB.

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Our primary finding showed a significant inverse relationship between $PM_{2.5}$ concentrations and TB risk at lower levels, while a positive relationship was observed at moderate to high $PM_{2.5}$ concentrations (Figure 2). Previous theoretical mechanisms suggested that $PM_{2.5}$ increases the risk of TB incidence. $PM_{2.5}$ is a mixture of many substances, including elemental carbon, organic carbon, metals and other substances. When we breathe in the air, after filtering particles above 10 μm in the upper respiratory airways, the residual $PM_{2.5}$ will enter the terminal bronchioles and alveoli. These $PM_{2.5}$ disrupt the balance of the immune system in the lungs and cause oxidative stress and reduction of endogenous antioxidants, which leads to the production of pro-inflammatory cytokines and ultimately cell injury or apoptosis.[33,34,35,36,37] This was considered to be one of the reasons why $PM_{2.5}$ increased susceptibility to TB.

To our knowledge, there is currently no theoretical mechanism supporting a protective effect of $PM_{2.5}$ on TB. In light of this, we conducted post-hoc analysis by constructing a restricted cubic spline regression for the population living outside mountain administrative areas, as a comparison group. When stratifying the population living outside mountain administrative areas, the previously observed U-shaped trend became less pronounced (*p*-values for non-linearity: 0.084 in complete population, 0.229 in living outside mountain administrative areas) (Appendix Figure S3). Living in mountain administrative areas was included as an alternative covariate to adjust for medical accessibility and TB control. According to government open data from the Taiwan Centers for Disease Control, neighboring townships in mountain administrative areas have a higher incidence rate of TB compared to urban districts. These townships may be part of the mountain administrative areas community. We hypothesize that the U-shaped

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association between $PM_{2.5}$ and TB, particularly the protective effect at lower concentrations, may be influenced by residual confounding. Further research is needed to confirm this hypothesis.

Additionally, our results also demonstrated a harmful effect of moderate to high concentrations of $PM_{2.5}$ on TB. $PM_{2.5}$ is often used as one of the tracers for cigarette smoke. Cigarette combustion generates a large amount of particulate matter and thousands of chemicals. Previous studies have estimated that the equivalent $PM_{2.5}$ concentration of current smoking ranges from 178 to 808 μg/m^3, with an adjusted odds ratio of 1.94 (CI: 1.01-3.73) for the incidence of TB.[38,39,40] The equivalent $PM_{2.5}$ concentration of passive smoking ranges from 20 to 50 μg/m^3, with a risk ratio of 1.59 (CI: 1.11-2.27) for the incidence of TB.[39,41,42] In our population, the average exposure concentration of $PM_{2.5}$ per individual per year during the follow-up period was 26.8 μg/m^3, which is much lower than the equivalent $PM_{2.5}$ concentrations of current and passive smoking. The risk of TB appears to decrease as the $PM_{2.5}$ equivalent concentrations decrease, which supports our findings.

We also observed age effect modification, which can be interpreted from two perspectives. Firstly, previous studies have reported age effect modification in chronic obstructive pulmonary disease (COPD).[19] Patients with COPD also have a high risk of developing TB.[43] If COPD is an intermediate between $PM_{2.5}$ and TB, then the age effect modification of COPD will also be reflected in our stratified analysis.[44,45,46,47] Secondly, in Kaohsiung, southern Taiwan, Wu et al. also found a higher TB reactivation rate in people aged 65 years or above.[48] The age effect modification we observed may reflect the differential risk of progressive primary and reactivation.[49]

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However, our study also has limitations that should be acknowledged. During the participant selection process, a total of 16,760 individuals were excluded due to missing data on at least one covariate. If these excluded individuals are at higher risk for developing TB, our results may be subject to selection bias. We expanded our exposure range using a nationally representative sample, but at the same time, we may have introduced spatial confounding. Even within urban areas, there were differences in the incidence rate of TB between the southern and northern regions. Our sample size was insufficient to support restricted cubic spline Cox regression analysis stratified by regions, which was an issue that we still needed to address. Another limitation of our study is the absence of individual whole genome sequencing information. In Taiwan, TB incidence in mountain administrative areas is suspected to be linked to progressive primary TB, while in urban areas, it is associated with reactivation TB. The observed U-shaped trend may indicate varying risks of $PM_{2.5}$ exposure on these two TB types. A recent study indirectly suggests that $PM_{2.5}$ could accelerate the reactivation of latent TB within the host by reporting an increased mutation rate of Mycobacterium tuberculosis in the presence of $PM_{2.5}$. Without access to individual whole genome sequencing information, it is challenging to determine whether $PM_{2.5}$ presents comparable risks for progressive primary TB and reactivation TB.

Our study utilized high-resolution $PM_{2.5}$ exposure data and accounted for changes in individual residential addresses during the follow-up period, aiming to re-evaluate the association between $PM_{2.5}$ and TB. The results revealed a nonlinear relationship between $PM_{2.5}$ and TB, particularly an inverse relationship at low levels. The elderly population might be the vulnerable subgroup for the effect of air pollution.

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Incorporating individual whole genome sequencing information in future studies will help clarify the relationship between $PM_{2.5}$ exposure and TB.

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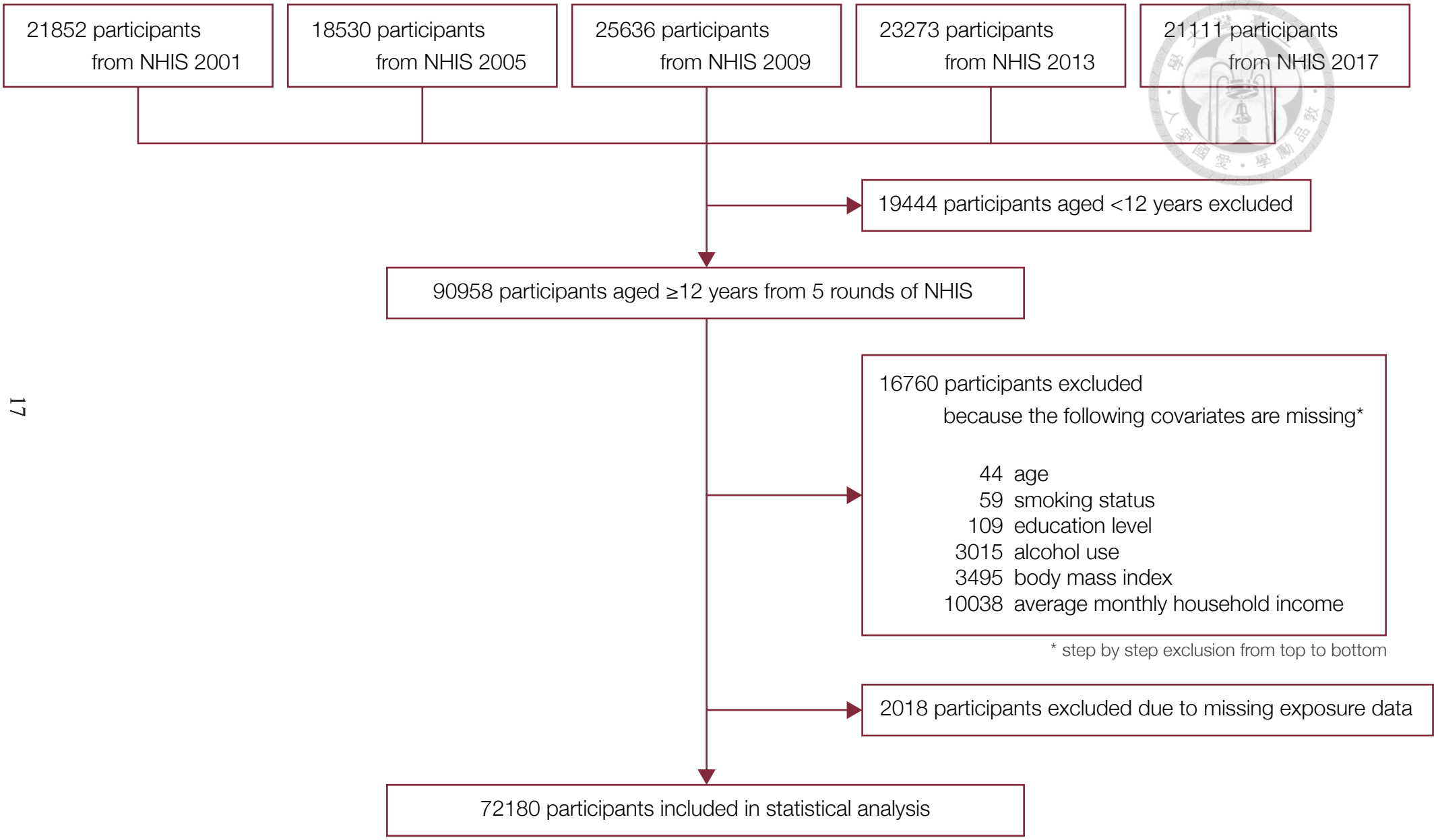
Figure 1



Flow diagram of participant selection. NHIS, National Health Interview Surveys.

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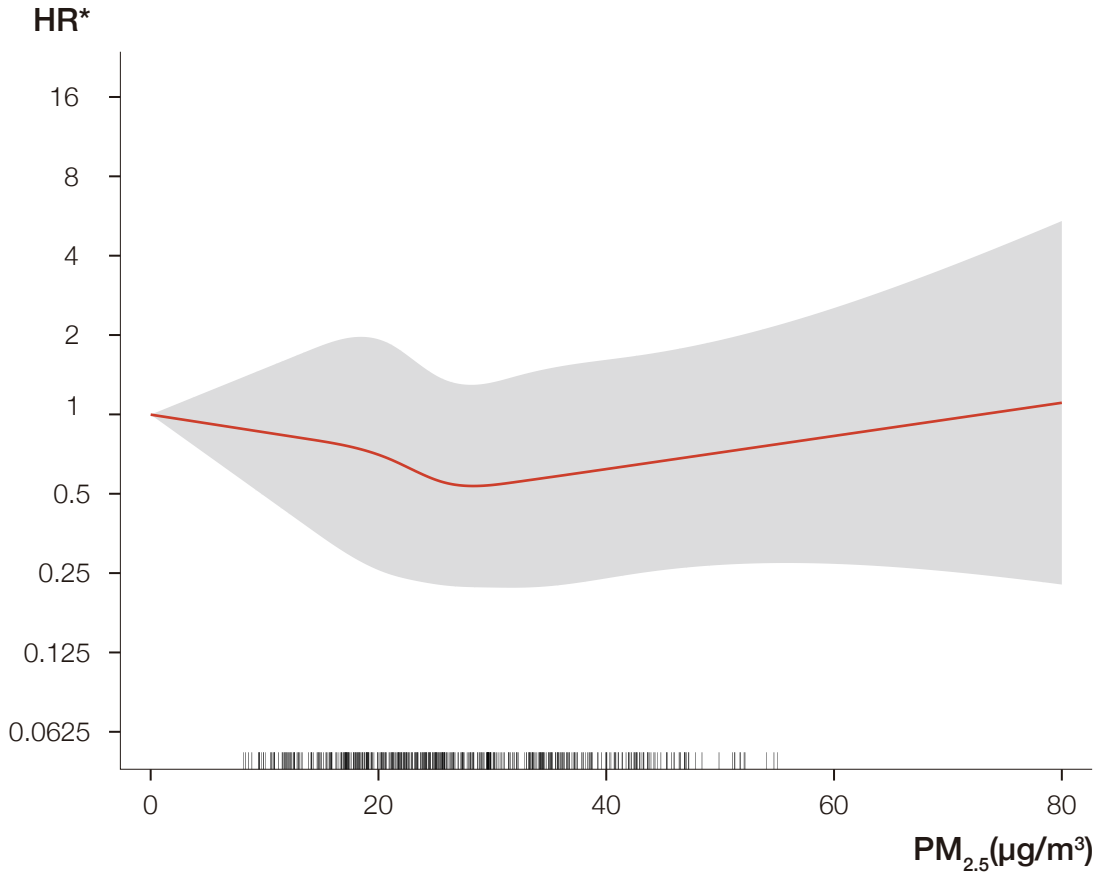
Figure 2



* adjusted for sex, age, body mass index, cigarettes smoking status, alcohol use, education level, average monthly household income, living in mountain administrative areas, TB history, and time varying calendar year

The relationship between $PM_{2.5}$ and hazard ratio by restricted cubic splines. Point estimates (red solid line) and 95% confidence intervals (gray band) are shown in the graph. The x-axis shows the distribution of exposure at onset of TB cases (average of the preceding two years).

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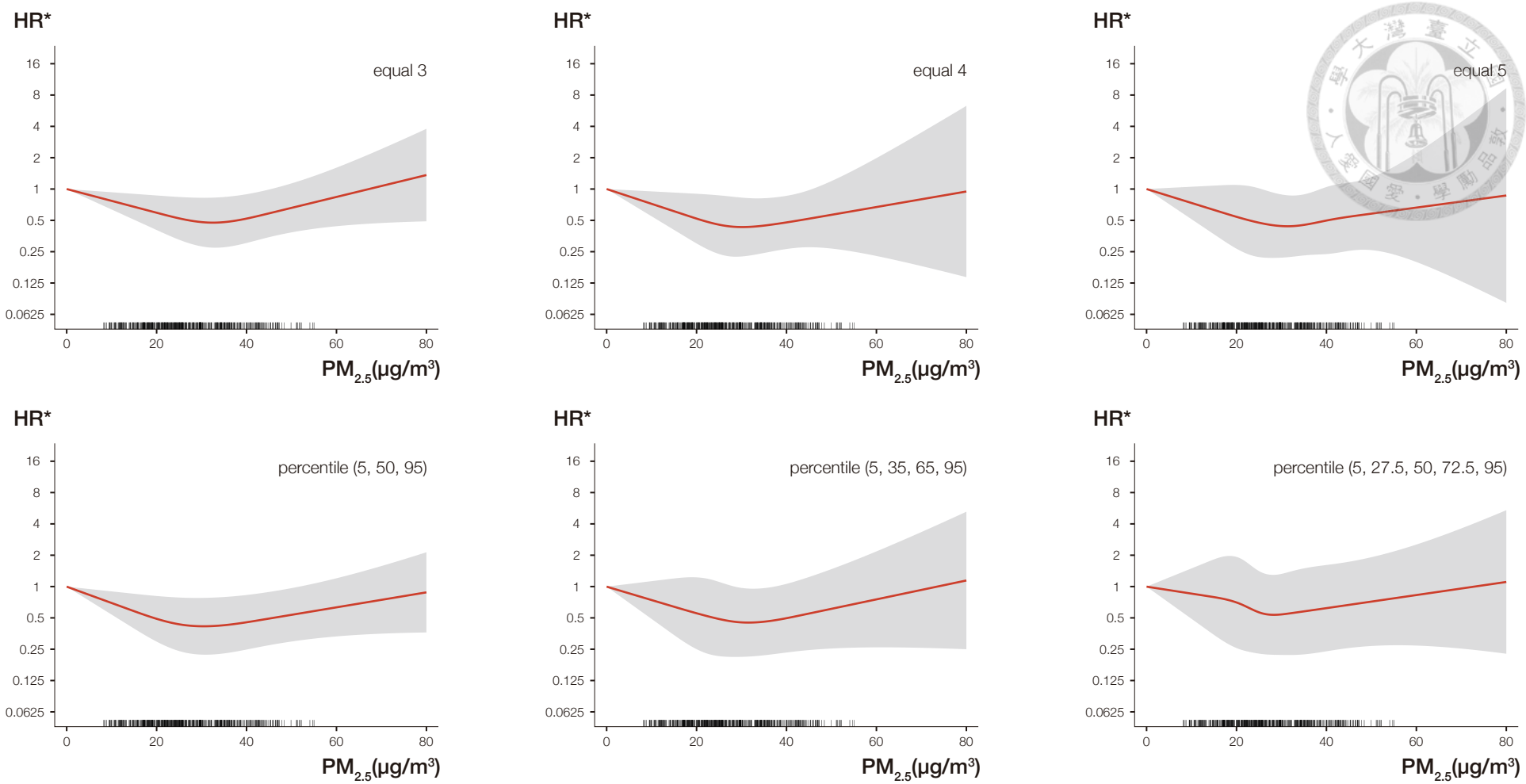
Figure 3



* adjusted for sex, age, body mass index, cigarettes smoking status, alcohol use, education level, average monthly household income, living in mountain administrative areas, TB history, and time varying calendar year

The performance of restricted cubic splines using different knot methods, from left to right and top to bottom, is as follows: equal 3, equal 4, equal 5, percentile (5, 50, 95), percentile (5, 35, 65, 95), and percentile (5, 27.5, 50, 72.5, 95). Point estimates (red solid line) and 95% confidence intervals (gray band) are shown in the graph. The x-axis shows the distribution of exposure at onset of TB cases (average of the preceding two years).

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Table 1. Distribution of study population characteristics during the first year of follow-up, stratified by quartiles of $PM_{2.5}$ exposure (average for the preceding 2 years)

Characteristics	1st quartile		2nd quartile		3rd quartile		4th quartile		Total		*p* -value
Exposure range[a]	8.37 < X ≦23.67		23.67 < X ≦30.16		30.16 < X ≦37.51		37.51 < X ≦56.65				
n	18070		18002		18238		17870		72180		
Sex											0.0891
male	9259	51.2%	9018	50.1%	9292	50.9%	8980	50.3%	36549	50.6%	
female	8811	48.8%	8984	49.9%	8946	49.1%	8890	49.7%	35631	49.4%	
Age[b] (standard deviation)	43.61	18.43	41.06	17.75	39.96	17.63	40.00	17.23	41.16	17.83	<.0001
BMI[c]											<.0001
underweight	1412	7.8%	1591	8.8%	1691	9.3%	1580	8.8%	6274	8.7%	
normal	10734	59.4%	11184	62.1%	11277	61.8%	11121	62.2%	44316	61.4%	
overweight	4679	25.9%	4188	23.3%	4213	23.1%	4207	23.5%	17287	23.9%	
obese	1245	6.9%	1039	5.8%	1057	5.8%	962	5.4%	4303	6.0%	
Cigarettes smoking status[d]											<.0001
never	13003	72.0%	13268	73.7%	13545	74.3%	13325	74.6%	53141	73.6%	
former	1205	6.7%	1041	5.8%	999	5.5%	793	4.4%	4038	5.6%	
current	3862	21.4%	3693	20.5%	3694	20.3%	3752	21.0%	15001	20.8%	
Alcohol use[e]											<.0001
never	10947	60.6%	11622	64.6%	11498	63.0%	12050	67.4%	46117	63.9%	
moderate	5679	31.4%	5309	29.5%	5557	30.5%	4450	24.9%	20995	29.1%	
excessive	1444	8.0%	1071	5.9%	1183	6.5%	1370	7.7%	5068	7.0%	
Education level											<.0001
junior or below	6939	38.4%	5919	32.9%	6565	36.0%	6843	38.3%	26266	36.4%	
high school	5518	30.5%	5618	31.2%	5746	31.5%	5932	33.2%	22814	31.6%	
college or ablove	5613	31.1%	6465	35.9%	5927	32.5%	5095	28.5%	23100	32.0%	
Average monthly household income											<.0001
<$30,000	4199	23.2%	3084	17.1%	3989	21.9%	4527	25.3%	15799	21.9%	
≥$30,000 and <$100,000	10470	57.9%	11191	62.2%	11377	62.4%	11052	61.8%	44090	61.1%	
≥$100,000	3401	18.8%	3727	20.7%	2872	15.7%	2291	12.8%	12291	17.0%	
TB history											0.004
yes	79	0.4%	53	0.3%	95	0.5%	63	0.4%	290	0.4%	
no	17991	99.6%	17949	99.7%	18143	99.5%	17807	99.6%	71890	99.6%	
Living in mountain administrative area											<.0001
yes	728	4.0%	114	0.6%	48	0.3%	47	0.3%	937	1.3%	
no	17342	96.0%	17888	99.4%	18190	99.7%	17823	99.7%	71243	98.7%	

a. X = $PM_{2.5}$ ($\mu g/m^3$)

b. mean (year)

c. body mass index: underweight <18.5, normal ≥18.5 and <25, overweight ≥25 and <30, and obese ≥30

d. nerver (never smoked, or <100 cigarettes in his or her lifetime), former (≥100 cigarettes in his or her lifetime, but had quit at the time of the interview), and current (≥100 cigarettes in his or her lifetime and currently smokes cigarettes)

e. never (never consumed a drink or had not consumed a drink in the past year), moderate (≤4 drinks per month in the past year), and excessive (>4 drinks per month in the past year)

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Table 2. Cox hazards regression estimated adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for associations of $PM_{2.5}$ concentrations with tuberculosis, preceding 2 years averages, within 5 rounds of National Health Interview Survey (NHIS). (n = 72180, events = 488, median follow-up = 11 years)

	Model 1[a]	Model 2[b]	Model 3[c]
Exposure[d]	1.10 (1.00, 1.22)	1.18 (1.07, 1.31)	0.94 (0.84, 1.05)
Sex			
male	2.36 (1.94, 2.86)	1.93 (1.54, 2.42)	1.86 (1.48, 2.33)
female	ref	ref	ref
Age[e]	1.06 (1.05, 1.07)	1.05 (1.05, 1.06)	1.06 (1.05, 1.06)
BMI[f]			
underweight		1.67 (1.21, 2.30)	1.68 (1.22, 2.32)
normal		ref	ref
overweight		0.68 (0.54, 0.84)	0.69 (0.55, 0.86)
obese		0.50 (0.30, 0.83)	0.53 (0.32, 0.90)
Cigarettes smoking status[g]			
never		ref	ref
former		0.96 (0.68, 1.35)	1.01 (0.72, 1.43)
current		1.47 (1.17, 1.85)	1.40 (1.11, 1.75)
Alcohol use[h]			
never		ref	ref
moderate		0.91 (0.71, 1.16)	0.97 (0.76, 1.24)
excessive		1.62 (1.26, 2.09)	1.63 (1.27, 2.10)
Education level			
junior or below		1.58 (1.16, 2.15)	1.44 (1.06, 1.96)
high school		1.38 (1.00, 1.91)	1.36 (0.98, 1.87)
college or ablove		ref	ref
Average monthly household income			
<$30,000		1.32 (1.08, 1.62)	1.43 (1.17, 1.75)
≥$30,000 and <$100,000		ref	ref
≥$100,000		0.97 (0.72, 1.32)	0.91 (0.67, 1.24)
TB history			
yes		10.15 (7.21, 14.28)	11.32 (8.04, 15.95)
no		ref	ref
Living in mountain administrative area			
yes		5.95 (4.29, 8.26)	3.61 (2.55, 5.12)
no		ref	ref
Calendar year[i]			0.89 (0.87, 0.92)

a. Model 1 adjusted for sex and age

b. Model 2 adjusted for sex, age, body mass index, cigarettes smoking status, alcohol use, education level, average monthly household income, living in mountain administrative areas, and TB history

c. Model 3 adjusted for the factors included in model 2 and time varying calendar year

d. for every 10μg/m^3 increase in $PM_{2.5}$ concentration

e. mean (year)

f. body mass index: underweight <18.5, normal ≥18.5 and <25, overweight ≥25 and <30, and obese ≥30

g. nerver (never smoked, or <100 cigarettes in his or her lifetime), former (≥100 cigarettes in his or her lifetime, but had quit at the time of the interview), and current (≥100 cigarettes in his or her lifetime and currently smokes cigarettes)

h. never (never consumed a drink or had not consumed a drink in the past year), moderate (≤4 drinks per month in the past year), and excessive (>4 drinks per month in the past year)

i. time varying numeric variable (year)

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Table 3. Cox hazards regression estimated adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) in the stratified analysis for associations of $PM_{2.5}$ concentrations with tuberculosis, preceding 2 years averages, within 5 rounds of National Health Interview Survey (NHIS).

	n	Events	Exposure mean[a]	Exposure SD[b]	HR[c]	95% CI	*p*-value[d]
Age							0.048
> 65 years	7864	186	29.50	9.81	1.09	(0.91, 1.31)	
≦ 65 years	64316	302	31.13	9.71	0.85	(0.73, 0.98)	
Sex							0.513
male	36549	342	30.87	9.73	0.96	(0.84, 1.10)	
female	35631	146	31.03	9.74	0.90	(0.72, 1.09)	
BMI[e]							0.150
≥ 25	50590	123	30.45	9.93	1.07	(0.86, 1.33)	
< 25	21590	365	31.16	9.65	0.90	(0.79, 1.03)	
Smoking							0.699
never	53141	267	31.08	9.70	1.00	(0.86, 1.16)	
former + current	19039	221	30.58	9.82	0.88	(0.75, 1.03)	
Living in mountain administrative area							0.133
yes	937	46	17.64	9.05	0.69	(0.46, 1.03)	
no	71243	442	31.13	9.63	0.99	(0.88, 1.12)	
NHIS survey year[g]							0.132
2001	15382	226	33.53	10.84	0.91	(0.78, 1.07)	
2005	14451	130	35.21	8.99	1.01	(0.80, 1.27)	
2009	16297	80	33.07	8.67	0.81	(0.59, 1.12)	
2013	14914	52	29.43	6.96	1.00	(0.64, 1.57)	

a. mean exposure during the first year of follow-up ($\mu g/m^3$)

b. standard deviation in exposure during the first year of follow-up ($\mu g/m^3$)

c. for every $10\mu g/m^3$ increase in $PM_{2.5}$ concentration

d. likelihood ratio test for the null hypothesis with no interaction term

e. body mass index

g. no incidents of tuberculosis in NHIS 2017

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Appendix

1.1 Air pollution definition

As defined by the WHO, air pollution is contamination of the indoor or outdoor environment by any chemical, physical or biological agent that modifies the natural characteristics of the atmosphere.[3] Outdoor air pollution is composed of a variety of substances, including various gases and fine solid or liquid particles suspended in the air.

2.1 National Health Interview Survey

NHIS is a routine cross-sectional interview survey conducted by Health Promotion Administration in Taiwan and National Health Research Institutes every four years since 2001. NHIS applied multistage stratified systematic sampling design to obtain a nationally representative sample. In stratification, sample were selected step by step following probability proportional to size sampling method. The target population for NHIS was noninstitutionalized Taiwan nationals with household registration in Taiwan (i.e. excluding residents in military, medical institutions, prisons and Taiwan nationals living in foreign countries) at the time of the interview. The sampling covered all municipalities, 11 counties (excluding Kinmen County and Lienchiang County), and all cities. NHIS respondents (response rate) were respectively 25464 (93.8) in 2001, 24726 (80.6) in 2005, 25636 (84.0) in 2009, 23296 (75.2) in 2013, and 21111 (72.8) in 2017.[9]

2.2 National Health Insurance Research Database

Medical information of Taiwan's residents who enrolled National Health Insurance system (NHI) was stored in NHIRD, including household registration, dates and

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location of visit or hospitalization, ICD-9-CM (International Classification of Diseases, Ninth Edition, Clinical Modification) before 2016, ICD-10 (International Classification of Diseases, Ten Edition) since 2016, detailed prescription records for each visit.[10] As of 2017, NHI covered 99.6% of Taiwan's residents, and contracted 92.74% of hospitals and clinics in Taiwan.[11]

2.3 Change of address

For each individual, the average exposure was estimated based on the address each year. Ku et al. proposed a method for estimating address using medical visit and household registration information in NHIRD.[12] The household registration information was updated monthly and the township with the most records in a year was used as the place of household registration for that year. If the most records had more than two townships, the township with the earlier month was used. The household registration information was collected from 1 January 2000 to 31 December 2019. Since 2001, if the household registration information was missing for that year, it was replaced with the previous year's information. For those records that are still missing, the information for the subsequent year was used instead.

Each individual's medical visit record was used to assign the place of medical visit for that year. For each year from 1 January 2000 to 31 December 2019, we collected information on the place of each individual's medical visits for acute respiratory infections (ICD-9-CM: 460-466 487 before 2016, ICD-10: J00-J06 J09-J11 J20-J22 since 2016). Consistent with the household registration assessment criteria, the township with the most records in a year was used as the place of medical visits for that

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year. In the absence of records of medical visits for acute respiratory infections, records of visits to local clinics, emergency, or outpatient departments were used instead.

The commute times provided by the Ministry of Transportation and Communications was used to determine the address for each individual. The 2016 National Well-Being Indicators mentioned that the average commute time for workers in Taiwan was 38 minutes, it was included in our threshold for address assessment. If the place of household registration was missing or outlying islands or commute time to the place of medical visits ≧ 38 minutes, then the place of medical visits was address, and conversely the place of household registration was address.

2.4 Anti-TB drugs for measurement of TB status

These were included first-line anti-TB drugs and drug-resistant TB treatment drugs, such as amikacin, kanamycin, cycloserine, ethambutol, streptomycin, isoniazid, rifampicin, rifabutin, rifamycin, pyrazinamide, prothionamide, para-aminosalicylate.[13] The following drugs were not included in the assessment because they were not provided by the NHI, such as ethionamide, capreomycin, gatifloxacin, bedaquiline, delamanid, terizidone, clofazimine.

2.5 Measurement of covariates

Previous studies suggested that smoking behavior increases the risk of TB.[14] We referenced the United States NHIS definition of cigarette smoking status: nerver (never smoked, or smoked less than 100 cigarettes in his or her lifetime), former (smoked at least 100 cigarettes in his or her lifetime, but had quit at the time of the interview), and

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current (has smoked 100 cigarettes in his or her lifetime and currently smokes cigarettes).[15]

Alcohol might inhibit immune response and increase susceptibility to TB.[16] We defined alcohol use in the following levels: never (never consumed a drink or had not consumed a drink in the past year), moderate (less than or equal to 4 drinks per month in the past year), and excessive (more than 4 drinks per month in the past year). Our definition of alcohol use levels differed slightly from the U.S. Centers for Disease Control and Prevention's criteria.[17]

TB was considered to be highly associated with the social environment.[18] Education level, and average monthly household income were included in our analysis as social mixing indicators. In Taiwan, the average monthly household income of less than $30,000 was regarded as low and middle income population.

Taiwan, like many other nations, experiences challenges related to health inequities, particularly in mountain administrative areas. These areas often face limited medical accessibility, which may contribute to the high incidence of TB in these communities. The Taiwan Tuberculosis Control Report 2020 shows that the incidence of TB in mountain administrative areas (113.4 per 100,000 people) is much higher than the national TB incidence (33.2 per 100,000 people).[19]

Participants were classified as having TB history with same criteria as ‘Measurement of TB status’, between 1 January 2000 and 31 December of the year before follow-up begins.

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Since the raw data for age, height and weight were numerical variables, we considered age ≥150, household size ≥100, height ≥300, weight ≥300, and BMI ≥200 as missing values. Information about sex, age, body mass index, education level, alcohol use, cigarettes smoking status, and average monthly household income was available from NHIS database, TB history and living in mountain administrative areas was available from NHIRD.

2.6 Statistical analysis

Expressed in mathematical form as follows:

The estimated concentrations of $PM_{2.5}$ in the *k*-th township from 2000 to 2020 are

$x_{0k}, x_{1k}, x_{2k}, x_{3k}, \ldots, x_{20k}, \quad k = 1,2,3,\ldots, 349$.

For the preceding 2 years average scale, one participant who followed up from 2002 to 2020, the exposure can be written by

$X_{2ij}, X_{3ij}, X_{4ij}, \ldots, X_{20ij}, \quad i = 1,2,3,\ldots, 349, \quad j = 1,2,3,\ldots, 349$,

where *i* is the *i*-th township of address for the first year, and *j* is the *j*-th township of address for the second year. Then they can be obtained by the following equation

$X_{2ij} = x_{0i} + x_{1j}, \quad X_{3ij} = x_{1i} + x_{2j}, \quad \ldots \quad X_{20ij} = x_{18i} + x_{19j}$.

$X(t) = \{x(u) : 0 \le u \le t\}, \quad G(t) = \{g(u) : 0 \le u \le t\}$

We use $X(t)$ to denote the value of $PM_{2.5}$ at time t, and to denote the history of $PM_{2.5}$ up to time t. Similarly, $G(t)$ to denote the calendar year at time t, and to denote its history up to time t.

$Z = \{x_1, x_2, x_3 \ldots\}$

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Z is the set of states of other covariates at the baseline. The conditional-hazard function of t given $X(t)$, $G(t)$ and Z is

$$\lambda(t \mid X(t), G(t), Z) = \lambda_0(t) e^{\beta X(t) + \delta G(t) + \gamma Z}$$

where $\lambda_0(t)$ is the baseline hazard function.

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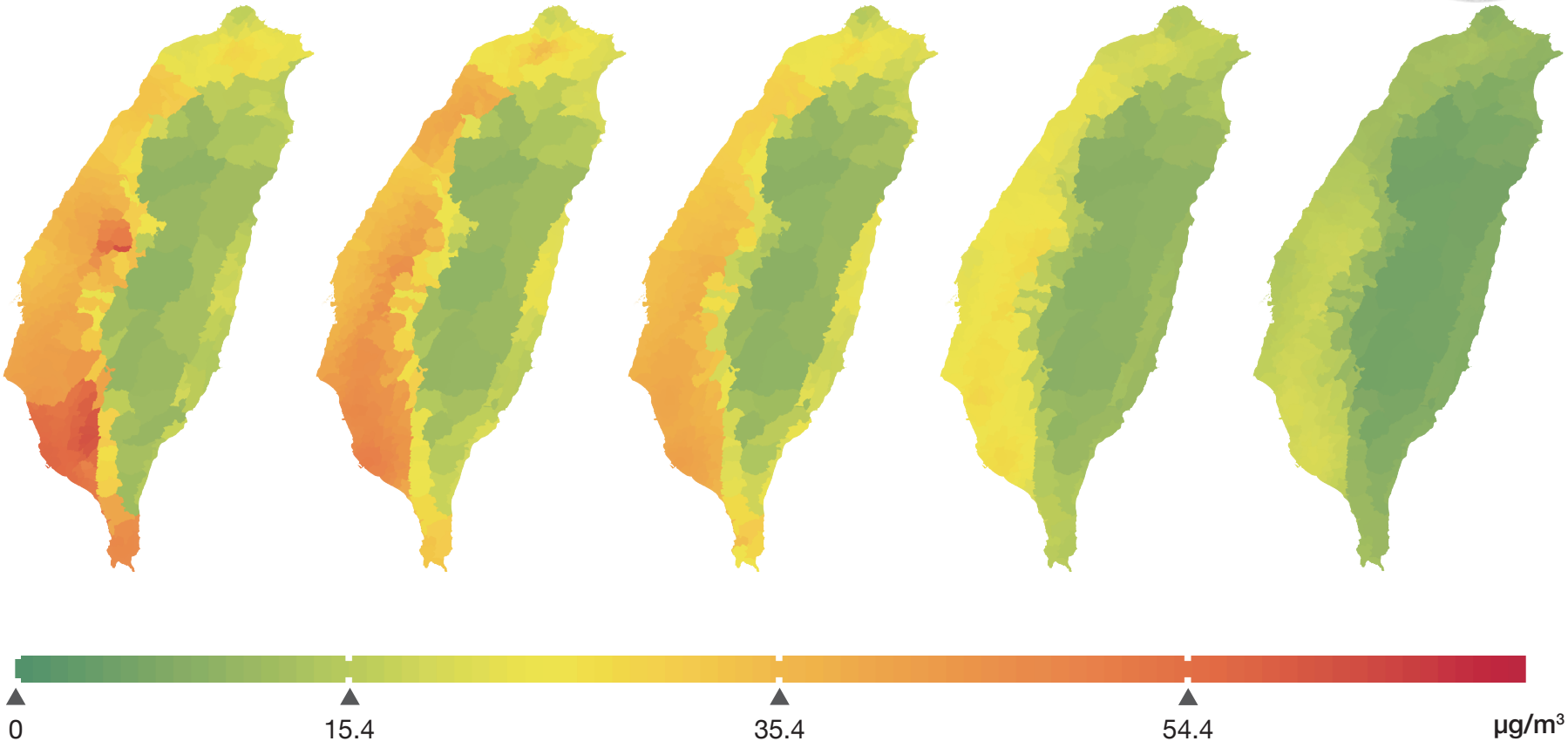
Figure S1



Spatial distribution of annual average $PM_{2.5}$ concentrations by township in 2000, 2005, 2010, 2015, and 2020 (left to right).

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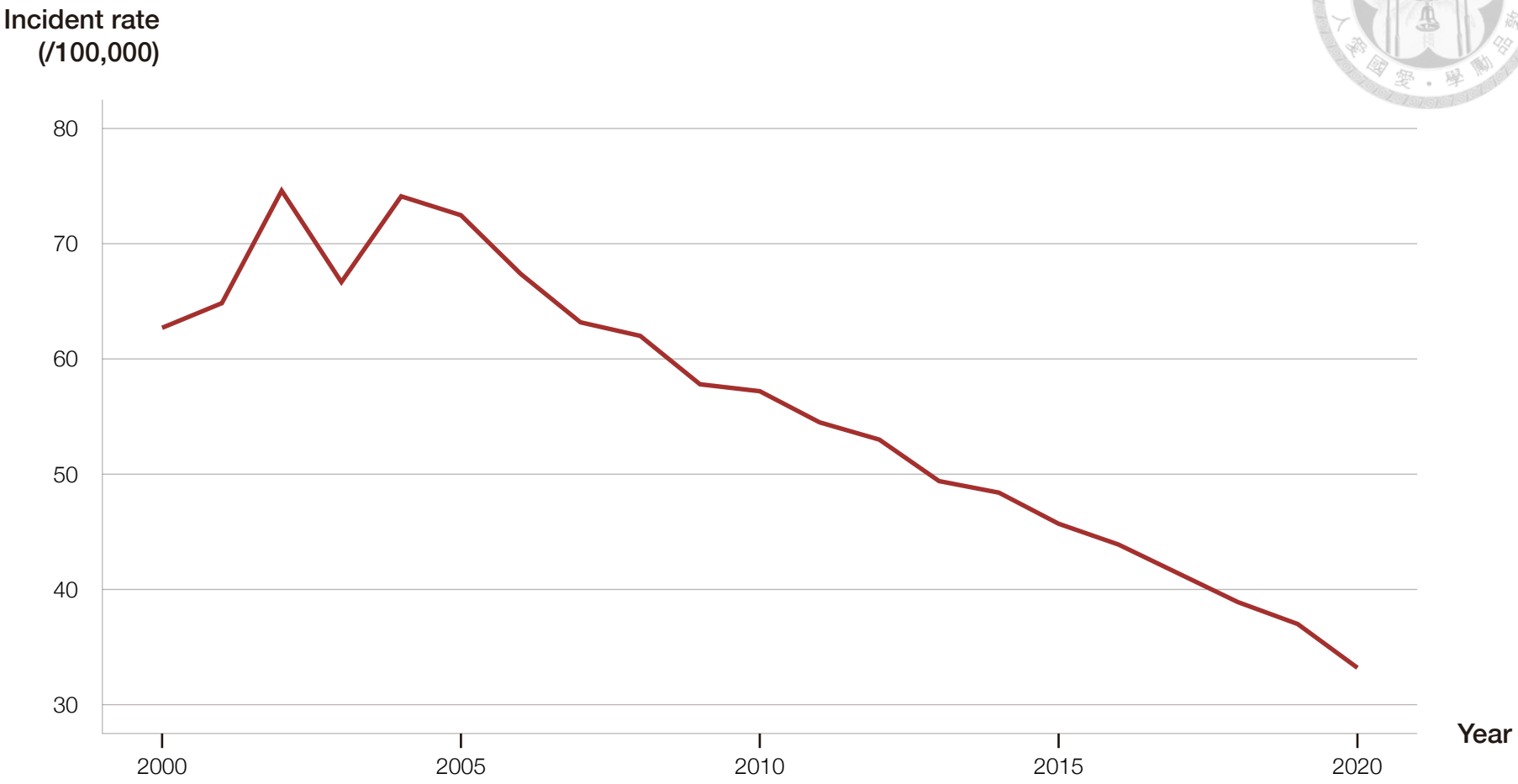
Figure S2



Trend of tuberculosis incident rate in Taiwan from 2000 to 2020 (per 100,000 population)

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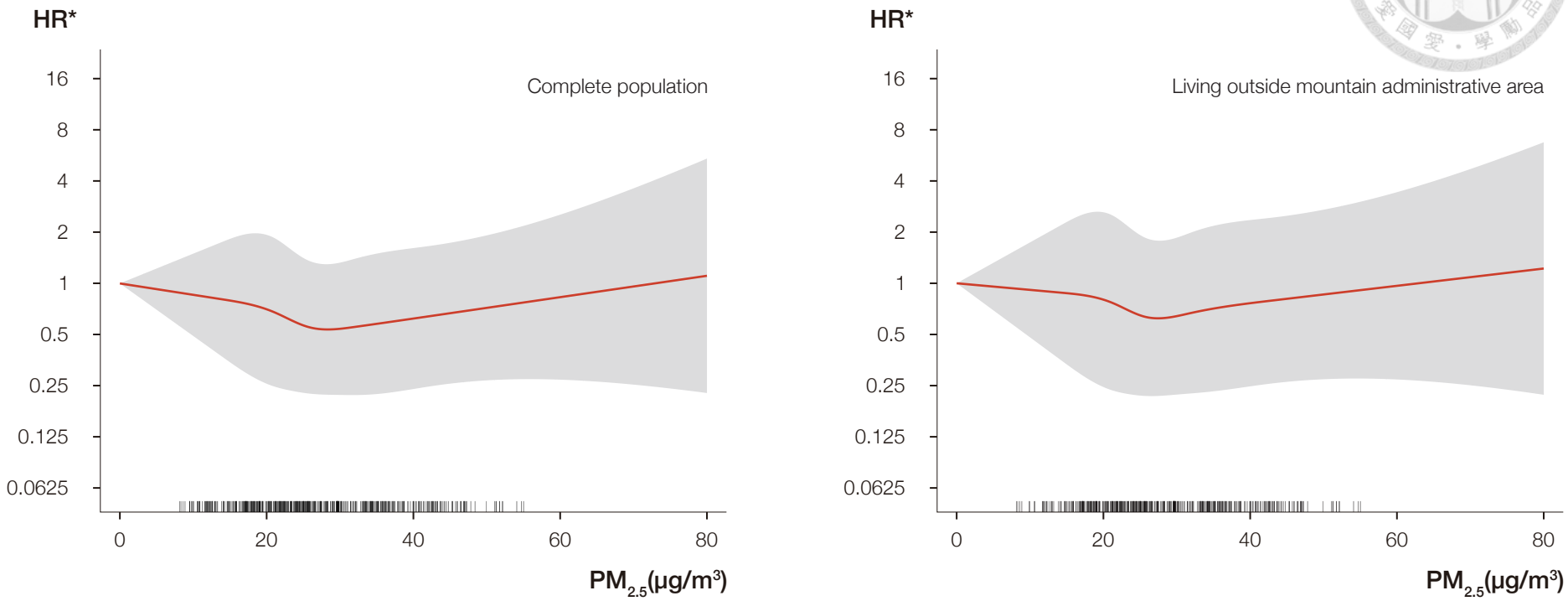
Figure S3



* adjusted for sex, age, body mass index, cigarettes smoking status, alcohol use, education level, average monthly household income, living in mountain administrative areas, TB history, and time varying calendar year

The comparison of hazard ratios by restricted cubic splines between the complete population and individuals living outside mountain administrative area. Point estimates (red solid line) and 95% confidence intervals (gray band) are shown in the graph. The x-axis shows the distribution of exposure at onset of TB cases (average of the preceding two years).

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Table S1. Evidence of the long-term effect (at least one year of exposure or lag) of $PM_{2.5}$ on tuberculosis prior to this study

Author, year	Location	Time frame	Study design	Tuberculosis measurement	Exposure assessment	Air pollutants	Results
Wu et al. 2022[1]	Kaohsiung, Taiwan	2012 - 2018	propensity-matched cohort with pneumonia (n=16,518) without pneumonia (match by age, sex, and comorbidities associated with tuberculosis, n=66,072)	ICD-9-CM codes in the participants' medical records	average concentration from the closest monitoring station throughout the follow-up period	$PM_{2.5}$ PM_{10} NO NO_2 NO_X SO_2 CO O_3	$PM_{2.5}$ ($1\mu g/m^3$) multi-pollutant adjusted* HR (95%CI) 1.13 (1.12, 1.15) *adjusted for age, sex
Lai et al. 2016[2]	New Taipei City, Taiwan	2005 - 2012	cohort (n=106,678)	microbiological confirmation and clinical suspicion	average concentration from the monitoring station closest to their residential address over the past 24 months	$PM_{2.5}$ PM_{10} NO_2 NO_X CO O_3	$PM_{2.5}$ ($10\mu g/m^3$) multi-pollutant adjusted* HR (95%CI) 1.39 (0.95, 2.03) *adjusted for age, sex, body mass index, education, marital status, alcohol use, smoking status, betel nut use, personal history of TB, history of TB in family, and median annual income
Smith et al. 2016[3]	Northern California, USA	1996 - 2010	nested case-control case (pulmonary tuberculosis, n=2,309) control (matched by age, sex, and race/ethnicity n=4,604)	microbiological confirmation and clinical suspicion	average concentration from the closest monitoring station throughout the 24 months prior to study entry	$PM_{2.5}$ PM_{10} NO_2 SO_2 CO O_3	$PM_{2.5}$ (5 quintiles, reference: the lowest quintile) single-pollutant / multi-pollutant adjusted* OR (95%CI) / adjusted* OR (95%CI) 1.13 (0.90, 1.41) / 1.17 (0.92, 1.49) 1.09 (0.87, 1.37) / 1.04 (0.84, 1.29) 1.11 (0.87, 1.42) / 1.10 (0.87, 1.39) 0.94 (0.73, 1.23) / 1.00 (0.83, 1.20) *adjusted for the matching factors (age, sex, and race/ethnicity)

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Liu et al. 2021[4]	Shandong province, China	2013 - 2017	ecological	microbiological confirmation and clinical suspicion	daily average concentration from monitoring stations	$PM_{2.5}$ NO_2 SO_2 CO O_3	$PM_{2.5}$ ($1\mu g/m^3$) multi-pollutant adjusted* IRR (95%CI) 1.03 (1.03, 1.03) *adjusted for meteorological information *lag 12 months with new infection TB (cumulative)
Carrasco-Escobar et al. 2020[5]	Lima, Peru	2015 - 2017	ecological	microbiological confirmation and clinical suspicion	annual global surface concentrations from NASA aerosol optical depth	$PM_{2.5}$	$PM_{2.5}$ (unknown unit) single-pollutant crude IRR (95%CI) adjusted* IRR (95%CI) 1.31 (1.15, 1.48) 1.32 (1.17, 1.50) *adjusted for poverty level
Yang et al. 2020[6]	Wulumuqi, China	2013 - 2017	ecological	People's Republic of China (ws288-2017)	monthly average concentration from the China National Environmental Monitoring Center	$PM_{2.5}$	$PM_{2.5}$ ($1\mu g/m^3$) single-pollutant adjusted* IRR (95%CI) 0.99 (0.99, 1.00) *adjusted for meteorological information *lag 12 months
Liu et al. 2018[7]	Jinan, China	2011 - 2015	ecological	microbiological confirmation and clinical suspicion	daily average concentration from the monitoring stations	$PM_{2.5}$ NO_2 SO_2 CO O_3	$PM_{2.5}$ ($10\mu g/m^3$) single-pollutant adjusted* IRR (95%CI) 0.95 (0.77, 1.17) *adjusted for meteorological information *lag 12 months

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Smith et al. 2013[8]	North Carolina, USA	1999 - 2007	ecological	microbiological confirmation and clinical suspicion	daily average concentration from the monitoring stations	$PM_{2.5}$	$PM_{2.5}$ (5 quintiles reference: the lowest quintile) single-pollutant crude IRR (95%CI) adjusted* IRR (95%CI) 1.38 (1.15, 1.66) 1.29 (0.97, 1.72) 1.28 (1.09, 1.50) 1.27 (1.00, 1.62) 1.13 (0.96, 1.32) 1.09 (0.86, 1.39) 1.34 (1.14, 1.56) 1.06 (0.80, 1.40) *adjusted for age, sex, race, year of diagnosis

IRR= incidence rate ratio HR= hazard ratio OR= odds ratio

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