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ORIGINAL RESEARCH

The Association of Latent Tuberculosis Infection with Air Pollutant Exposure, Meteorological and Other Factors: A Retrospective Study in Eastern China of College Students

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Objective: The associations between meteorological factors, air pollutant indicators, and latent tuberculosis infection (LTBI) have not yet been confirmed. This study aimed to assess the association of meteorological factors, air pollutant indicators, and other factors with LTBI among college students.

Methods: We selected 5,193 freshmen randomly who originated from key tuberculosis areas in nine colleges in Nanjing. We ranked the importance of independent variables using Least Absolute Shrinkage and Selection Operator (LASSO) regression and random forest models. We then conducted a multi-model analysis after incorporating them into the prediction model. In addition, we adopted a calibration curve to determine the quality of the model. A nomogram was used to evaluate the possibility of using multiple models to predict LTBI risk.

Results: We found that higher outdoor PM_{10} concentrations (OR: 1.35; 95% CI: 1.10–1.65) was associated with LTBI. A history of allergies (OR: 1.37; 95% CI: 1.16–1.62) and coal-based fuels (OR: 1.44; 95% CI: 1.11–1.87) had a positive correlation with the occurrence of LTBI. Taking vitamin D supplements (OR: 0.82; 95% CI: 0.69–0.98) could reduce the risk of LTBI. Besides, age (OR: 1.11; 95% CI: 1.00–1.22) were significantly associated with strong positive populations.

Conclusion: Higher outdoor PM_{10} concentration, history of allergies, and use of coal-based fuels were positively correlated with the occurrence of LTBI. Vitamin D supplementation might reduce the risk of LTBI. Besides, older people were more likely to contribute to strong positive results.

Keywords: latent tuberculosis infection, PM_{10}, vitamin D, household fuel, allergy

Introduction

According to the Global Tuberculosis Report 2024 issued by the World Health Organization (WHO),[1] there are 10.8 million new tuberculosis patients in 2023 globally with an incidence rate of 134/100000. Latent tuberculosis infection (LTBI) refers to a state of continuous immune response to stimulating *Mycobacterium* tuberculosis antigen (Ag); however, there are no obvious clinical signs or symptoms of active tuberculosis (ATB).[2,3]

It is estimated that 1/4 of the population is infected with *Mycobacterium* tuberculosis worldwide, of which approximately 5% −10% will develop ATB[4,5] in their lifetime (usually within 2 years after exposure). LTBI is considered the main source of new ATB cases and remains the main obstacle to achieving the World Health Organization's goal of ending tuberculosis prevalence.[6] Among them, the elderly, adolescents, human immunodeficiency virus (HIV) patients, diabetes patients, and people with primary immunodeficiency and immunosuppression are at a higher risk of LTBI.[7–10]

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The "Guidelines for the Management of Latent Tuberculosis Infections" released by WHO in 2015 pointed out that the above-mentioned population needs to undergo systematic testing and treatment for LTBI.[11] Approximately 350 million people in China are infected with *Mycobacterium* tuberculosis,[4,12] making it the country with the highest burden of latent tuberculosis infections worldwide.

LTBI is established through finely regulated immune responses in most *Mtb*-infected individuals.[13] Significant differences in immune cell abundance were observed between the LTBI and ATB cohorts. Studies have shown that the proportion of CD8 T cells, resting and activated CD4 memory T cells, and γδT cells was higher in the LTBI group, whereas the proportion of neutrophils, monocytes, and M0 macrophages was lower.[14,15]

Fortunately, the government has attached great importance to the prevention and treatment of tuberculosis among its students. To prevent tuberculosis infection in the school environment and spread in the school, health examinations including tuberculin skin test/gamma interferon release test, chest X-ray examination, etc., are carried out for students and teaching staff.[12] Schools have become high-risk environments for the spread of TB because of their dense population and close contact. The annual enrollment of new students can be regarded as a large-scale migration, and the flow of students from high-incidence areas to low-incidence areas may lead to the spread of tuberculosis between different regions.[16] However, most patients with LTBI in China have not received Tuberculosis preventive therapy (TPT). Previous studies have shown that stigma, adverse drug reactions, and lack of knowledge about tuberculosis are reasons for the failure of TPT.[15]

The incidence rate of tuberculosis reported by students in China is about 1/3 of the incidence rate reported by the whole population, especially in the age group around 18 years, which accounts for the highest proportion. According to the China Information System for Disease Control and Prevention, student TB patients accounted for 4.02% of total TB patients in 2014.[17] Among students group, geographical area is an important factor affecting LTBI.[18] A study in Beijing showed that the detection rate of LTBI among freshmen is as high as 11.6%.[16] Tuberculosis screening and preventive treatment are important components of school tuberculosis prevention and control strategies.[15,19] Therefore, effective management of asymptomatic carriers with the highest risk of progression and transmission is currently an important clinical and public health challenge.

The purpose of our study was to combine LASSO regression and random forest models to sort the characteristic variables and build a predictive model. The risk factors affecting the occurrence and development of LTBI were analyzed to provide clues for epidemiological studies on LTBI. Our study provides guidance to reduce the risk of LTBI.

Methods

Study Design and Population

Nanjing, located in Jiangsu Province, China, is the province's capital city. There are 52 colleges in Nanjing, ranking high in China (end of 2024).

According to the National School Tubulosis Prevention and Control Guidelines,[20] all participants were from provinces with a high incidence rate of tuberculosis who needed to undergo LTBI screening. This study enrolled epidemiological data from college students who participated in screening for LTBI in Nanjing in 2024. There were a total of 9 colleges under the jurisdiction of five districts: JiangNing, JiangBei, QiXia, PuKou, and LiShui. We chose the cluster random sampling method to select samples. Tuberculin skin test(TST) was used as a screening method for LTBI. We selected a purified protein derivative (PPD) as the screening method in this study, owing to its low cost, simple operation, and high sensitivity. This method is suitable for screening LTBI in large populations. A questionnaire survey was conducted to collect relevant information from students who had undergone PPD.

Data Source

We collected basic information from all students using a questionnaire. The questionnaire content included gender, age, ethnicity, tuberculosis history, tuberculosis contact history, medical history, accommodation history, residential environment disinfection, and sunshine ventilation.

We obtained PPD skin test results from the students. 0.1 mL of PPD preparation was injected intradermally at l/3 above the curved side of the left forearm, and the results were examined within 48–72 h. Results: (1) Negative: average diameter of the induration < 5 mm or without response; (2) generally positive: average diameter between 5 and 10 mm; (3) moderately positive: average diameter between 10 and 15 mm; (4) strongly positive: ≥15 or <15 mm but with double rings, blisters, necrosis, and lymphangitis.

According to national guidelines (WS288-2017), the PPD reaction with a hardened diameter ≥ 10 mm is defined as LTBI.

In addition, we extracted meteorological data and outdoor air pollutant concentrations, including the provinces from which the students came. The time range was the annual average concentration from 2016 to 2023. The concentrations of outdoor air pollutants were PM_{10} (μg/m^3), $PM_{2.5}$ (μg/m^3), SO_2 (μg/m^3), NO_2 (μg/m^3), CO (mg/m^3), and O_3 (μg/m^3). Meteorological data included average temperature (°C), average relative humidity (%), and average wind speed (m/s).

Statistical Analysis

This study used LTBI and PPD reactions with hardened diameters ≥ 10 and 15 mm as dependent variables, combined with demographic variables, meteorological data, and air pollution data to establish a predictive model. We ranked the importance of independent variables using LASSO regression and random forest models. We then conducted a multimodel analysis after incorporating them into the prediction model. Odds ratios (OR) and the corresponding 95% confidence intervals (CIs) were calculated. The above analyses were conducted the R 4.4.2 (http://www.r-project.org). *P*-values <0.05 were considered statistically significant in our analyses. In addition, we adopted a calibration curve to determine the quality of the model. A nomogram was used to evaluate the possibility of using multiple models to predict LTBI risk.

Results

Characteristics of Participants

Originally, 6826 students underwent PPD skin tests. Excluding missing, abnormal, and extreme data, the study ultimately included 5193 participants as the study population. Among them, 936 (18.02%) were diagnosed with LTBI, and the remaining 4257 (81.98%) were excluded (Figure 1).

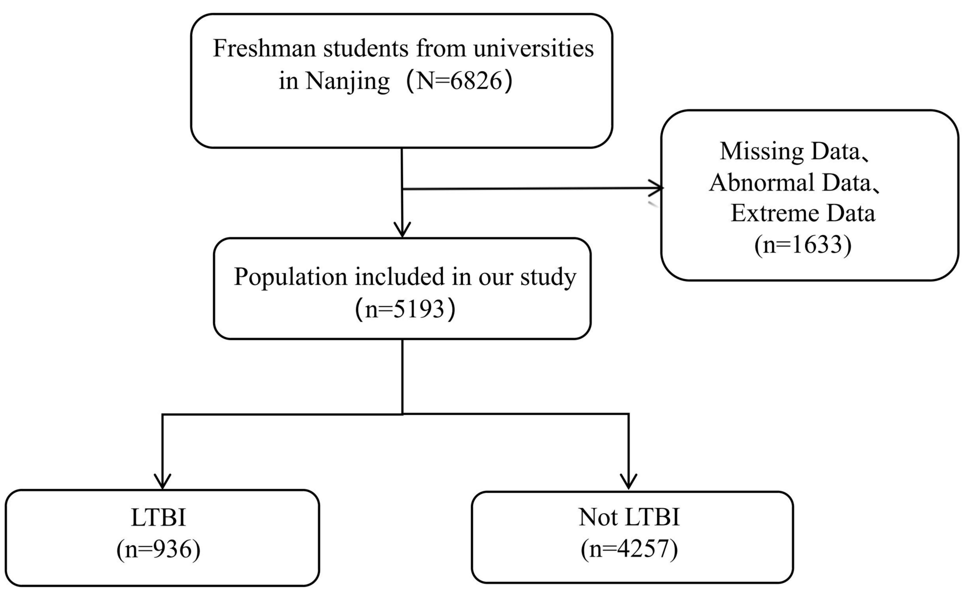

Figure 1 Flowchart of Participants Enrolled in the Study.

Demographic Information

A total of 2197 males (42.31%) and 2996 females (57.69%) were included in our study. In total, 212 participants (4.08%) had a history of TB exposure. The number of people of the Han ethnicity was 3616 (69.63%). Furthermore, there were 1166 students (22.45%) consumed Vitamin D. In terms of household fuel, 402 (7.74%) students' families used biofuels such as coal, firewood, and straw. 2629 (50.63%) people utilized natural gas, whereas the remaining 2162 (41.63%) used electricity. In terms of their major, 538 participants were engaged in medicine. Other 4655 people were non-medical. The median age (interquartile range(IQR)) was 18 (15–38) (Table 1).

The distribution of participants' registered residences was as follows: 99 from Gansu (1.91%), 124 from GuangXi (2.39%), 1763 from Guizhou (33.95%), 49 from NingXia (0.94%), 219 from QingHai (4.22%), 1001 from SiChuan (19.28%), 188 from XiZang (3.62%), 640 from XinJiang (12.32%), 739 from YunNan (14.23%), and 371 from Chongqing (7.14%).

Factors Related to LTBI

We performed a graphical test (P-P plot) for age in 5193 participants, which showed an integral normal distribution.

We conducted univariate logistic regression analysis for each factor, and the results are shown in Table S1 and Table 2. The possibility of LTBI would increase when the concentration of Pm_{10} (OR: 1.36; 95% CI: 1.11–1.65), average relative humidity (OR: 1.20; 95% CI: 1.04–1.38), CO (OR: 1.60; 95% CI: 1.03–2.49) and NO_2 elevate (OR: 1.36; 95% CI: 1.11–1.65); Compared with the population who did not have the usage of Vitamin D, people with taking Vitamin D reduced the prevalence of LTBI (OR: 0.82; 95% CI: 0.69–0.98); There was a high association between a history of allergies (OR: 1.39; 95% CI: 1.18–1.64) and household fuel of coal and others (OR: 1.43; 95% CI: 1.10–1.86) with LTBI. We found an interaction between professional type and LTBI (OR: 0.72; 95% CI: 0.58–0.90).

We selected the top 15 random forest model importance rankings and the intersection of LASSO regression model results as feature variables, and forcibly included variables with *P*-values<0.05 in univariate analysis, and temperature to construct a prediction model. The selection process for variables in the LASSO regression model is shown in Figure 2. The importance rankings of random forest model variables are shown in Figure 3. The results are presented in Table S1 and Table 2. Stepwise regression was adopted for multicollinearity was existed in the multivariate model of LTBI. We found that male (OR: 1.18; 95% CI: 1.02–1.36) was more likely to contribute to LTBI; Higher outdoor PM_{10}

Table 1 Demographic Information in the Study

Variables		Numbers	Percentage (%)
Gender	Male	2197	42.31
	Female	2996	57.69
Ethnicity	Han	3616	69.63
	Non-Han	1577	30.37
Professional type	Medicine	538	10.36
	Non -medicine	4655	89.64
History of tuberculosis	Yes	20	0.39
	No	5173	99.61
Contact history of tuberculosis	Yes	212	4.08
	No	4981	95.92
Allergic history	Yes	1076	20.72
	No	4117	79.28
Boarding history in high school	Yes	1125	21.66
	No	4068	78.34
Usage of Vitamin D	Yes	1166	22.45
	No	4027	77.55
Household fuel types	Electricity	2162	41.63
	Natural gas	2629	50.63
	Coal and others	402	7.74

Table 2 Univariate and Multivariable Analysis Based on Multiple Models of Epidemiological Characteristics Associated With Moderately Positive Participants

Variables		Univariate Analysis		Multivariate Analysis	
		Cor (95% CI)	*P*-Value	Aor (95% CI)	*P*-Value
Age		1.02(0.97–1.07)	0.495		
Gender	Male	1.14(0.99–1.31)	0.080	1.18(1.02–1.36)	0.026*
	Female	Reference		Reference	
Ethnicity	Han	1.09(0.93–1.27)	0.299		
	Non-Han	Reference			
Professional type	Medicine	Reference		Reference	
	Non -medicine	0.72(0.58–0.90)	0.003	0.73(0.59–0.91)	0.005*
PM_{10} (μg/m^3)	≤40	Reference		Reference	
	>40	1.36(1.11–1.65)	0.003	1.35(1.10–1.65)	0.004*
$PM_{2.5}$ (μg/m^3)	≤35	Reference			
	>35	1.09(0.94–1.26)	0.243		
Average temperature (°C)	≤20°C	Reference			
	>20°C	1.15(0.71–1.86)	0.579		
Average relative humidity (%)	≤75	Reference			
	>75	1.20(1.04–1.38)	0.013		
Average wind speed (m/s)	≤2.5	Reference			
	>2.5	0.63(0.40–0.97)	0.037		
AQI	≤40	Reference			
	>40	1.36(1.11–1.65)	0.003		
SO_2 (μg/m^3)	≤15	Reference			
	>15	1.14(0.87–1.49)	0.335		
CO (mg/m^3)	≤0.6	Reference			
	>0.6	1.60(1.03–2.49)	0.037		
NO_2 (μg/m^3)	≤18	Reference			
	>18	1.36(1.11–1.65)	0.003		
BCG	Yes	1.39(1.05–1.83)	0.020		
	Unknown	1.04(0.76–1.45)	0.794		
	Self-statement: None	Reference			
History of tuberculosis	Yes	Reference			
	No	0.41(0.16–1.02)	0.056		
Contact history of tuberculosis	Yes	0.94(0.66–1.34)	0.744		
	No	Reference			
History of mental illness	Yes	1.07(0.59–1.95)	0.834		
	No	Reference			
Allergic history	Yes	1.39(1.18–1.64)	0.001	1.37(1.16–1.62)	0.001*
	No	Reference		Reference	
Smoking history	Yes	Reference			
	No-quit smoking	0.97(0.54–1.75)	0.918		
	Never	0.78(0.56–1.09)	0.139		
Smoking history of cohabitants	Yes	1.05(0.88–1.25)	0.614		
	No	Reference			
Smoking type	None	Reference			
	Cigarette	0.86(0.54–1.36)	0.513		
	Electronic cigarette	0.88(0.57–1.38)	0.583		
Drinking history	No	Reference			
	Occasionally	0.61(0.31–1.20)	0.151		
	Frequently	0.57(0.29–1.12)	0.101		
Boarding history in high school	Yes	1.08(0.91–1.28)	0.370		
	No	Reference			
Number of cohabitants in family		1.01(0.95–1.07)	0.854		

(*Continued*)

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Table 2 (Continued).

Variables		Univariate Analysis		Multivariate Analysis	
		Cor (95% CI)	*P*-Value	Aor (95% CI)	*P*-Value
Usage of household air purifiers	Yes	0.97(0.82–1.16)	0.768		
	No	Reference			
Regular disinfection of households	Yes	Reference			
	No	0.93(0.80–1.08)	0.332		
Number of classmates in high school	<50	0.70(0.42–1.17)	0.175		
	50–60	0.76(0.46–1.27)	0.299		
	60–70	0.75(0.42–1.33)	0.321		
	>70	Reference			
Household fuel types	Electricity	Reference		Reference	
	Natural gas	1.15(0.99–1.34)	0.065	1.13(0.97–1.31)	0.123
	Coal and others	1.43(1.10–1.86)	0.007	1.44(1.11–1.87)	0.007*
Usage of Vitamin D	Yes	0.82(0.69–0.98)	0.030	0.82(0.69–0.98)	0.031*
	No	Reference		Reference	
Sunshine situation of high school classrooms	Yes	1.04(0.84–1.28)	0.741		
	No	Reference			

Notes: *The *P*-value of the multivariate analysis was≤0.05.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval.

concentrations (OR: 1.35; 95% CI: 1.10–1.65) had a positively correlation with LTBI. A history of allergies (OR: 1.37; 95% CI: 1.16–1.62) and coal-based fuels (OR: 1.44; 95% CI: 1.11–1.87) were also significantly associated with the occurrence of LTBI. In addition, we found that taking vitamin D supplements (OR: 0.82; 95% CI: 0.69–0.98) can reduce the risk of LTBI; Professional type (OR: 0.73; 95% CI: 0.59–0.91) was also associated with LTBI.

In addition, we expanded the threshold for PPD testing to 15 mm, which is a strongly positive population. The results showed that age (OR: 1.11; 95% CI: 1.00–1.22) were significantly associated with strong positive populations. Interestingly, regular disinfection at home (OR: 0.76; 95% CI: 0.58–0.99) was contributed to strong positive cases. This might be related to the conscious increase in the frequency of disinfection by family contacts of tuberculosis.

Prediction of the Risk of LTBI

Furthermore, a calibration curve was used to reflect the quality of the model predictions. The mean absolute error was 0.006, which is relatively low. Our study attempted to use the nomogram to clinically predict the risk of LTBI using associated indicators. A population nomogram prediction model was constructed based on six variables including gender, allergic history, type of household fuel, Vitamin D usage, professional type and Pm10 according to multivariate logistic regression analysis. The results are shown in Figure 4. Each variable was assigned a score ranging from 0 to 100. The scores of each variable were summarized. The total score was determined based on the individual scores calculated using the nomogram; most participants in the present study had the risk of LTBI ranged from 10% to 30%.

Discussion

To our knowledge, this study is the first to investigate the association between meteorological factors, air pollutants, and LTBI in Chinese college students. Through a comprehensive analysis of the Lasso regression and random forest models, our study results showed that high outdoor concentrations of PM_{10}, allergy history, and coal-based biofuels increased the risk of LTBI. Male population and Vitamin D supplements could reduce the risk of LTBI. For strongly positively infected individuals, the results revealed an association between age, professional type, allergic history, and charcoal-based biofuels. Vitamin D supplements can reduce the risk of strongly positive infection. This is highly consistent with the results of the LTBI. Interestingly, regular disinfection at home was contributed to strong positive cases. This might be related to the conscious increase in the frequency of disinfection by family contacts of tuberculosis.

In recent years, to achieve the goal of ending tuberculosis promoted by the WHO as soon as possible, countries with a high burden of tuberculosis have carried out screening tests for high-risk groups with LTBI according to their

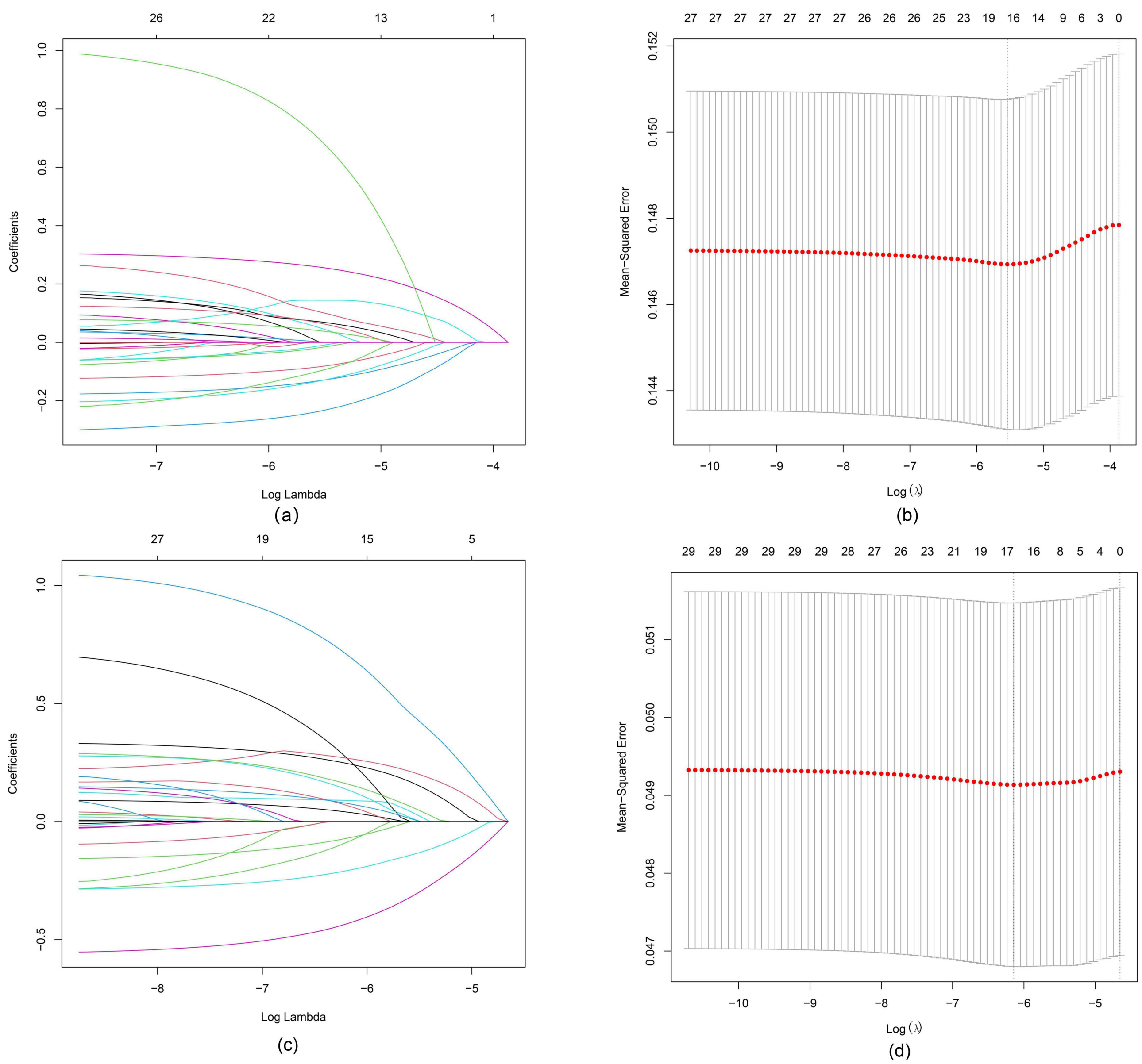

Figure 2 LASSO Regression of Risk Factors. (**a**) Ten-time cross-validation for Tuning Parameter Selection in the LASSO model. (**b**) LASSO coefficient profiles of risk factors for moderately positive participants. (**c**) Ten-time cross-validation for Tuning Parameter Selection in the LASSO model. (**d**) LASSO coefficient profiles of risk factors for strongly positive participants.

national conditions. A cross-sectional study on the 2011–2012 NHANES population data showed that current smoking was associated with LTBI. Household contact with TB was also related to LTBI.[2] A population-based multicenter cohort study found that an increment of 5 μg/m^3 in 2-year moving averaged $PM_{2.5}$ was associated with a 50.6% increased risk of active TB.[7] Another study suggested that outdoor PM concentrations were positively correlated with LTBI risk.[21] These results were consistent with our findings. Some blood indicators, such as phthalate metabolites,[22] blood metals[8] and methyl mercury[23] have been associated with an increased prevalence of LTBI. In terms of socioeconomic factors, previous studies have shown that LTBI is associated with a low education level, old age, male sex, marital status, history of hyperlipidemia, and history of diabetes.[22,24] Climate change is a major threat to human health in the 21st century. Changes in climatic factors have a significant impact on the incidence and burden of tuberculosis.[25,26] The human body is influenced by various meteorological conditions and varying degrees of humidity can affect the heat resistance threshold. The incidence of tuberculosis presents seasonal changes for a long time. We

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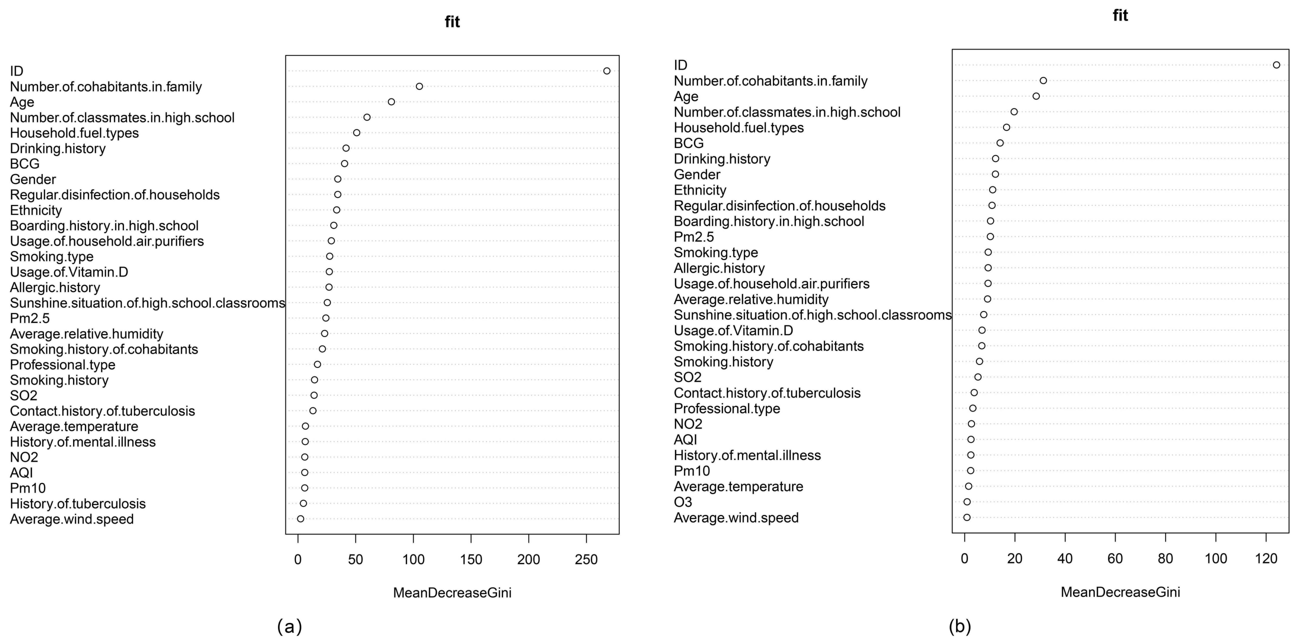

Figure 3 Variable Importance of Risk Factors based on Random Forest Model. (**a**) Variable importance of risk factors based on random forest model for moderately positive participants. (**b**) Variable importance of risk factors based on random forest model for strongly positive participants.

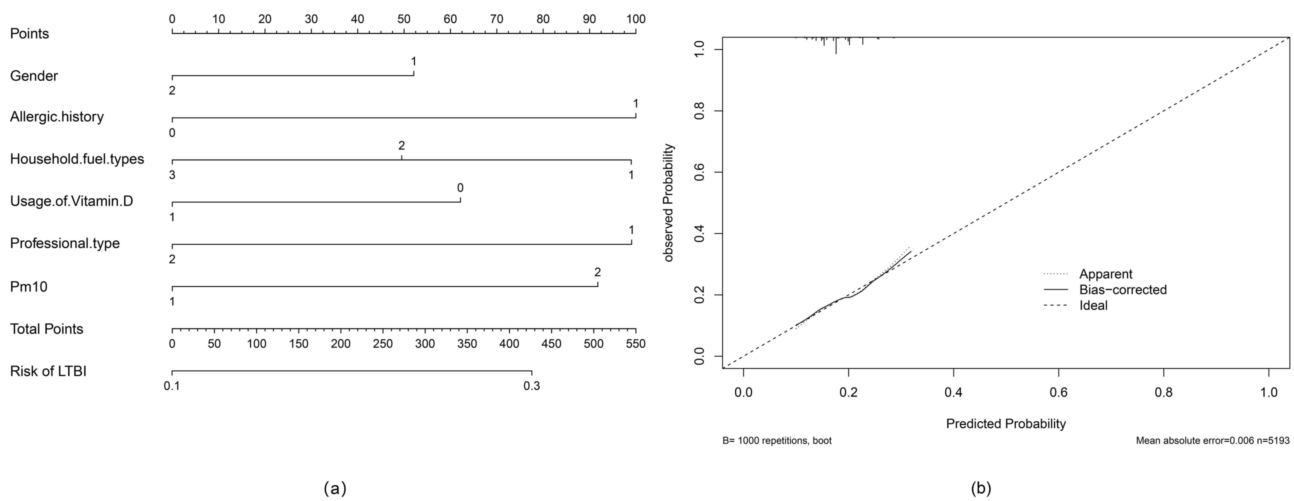

Figure 4 Nomogram of Predicting the Risk of Latent Infection of Tuberculosis and Calibration Curve of multiple Models. (**a**) Nomogram of predicting the risk of Latent Infection of Tuberculosis. (**b**) Calibration curve of multiple models.

speculated that this may be related to environmental factors.[27] Therefore, understanding the temporal and spatial correlations between meteorological factors and tuberculosis incidence can provide important information for developing targeted tuberculosis intervention measures. Some studies have indicated that temperatures that are too high or too low increase the risk of tuberculosis. Increased humidity and precipitation increases the risk of tuberculosis. A nationwide epidemiological study in China found that low temperature (<16.69°C), high relative humidity (>71.73%), and low sunshine hours (<6.18 h) increased the risk of tuberculosis, while extremely low wind speed (<2.79 m/s) reduced the risk of it.[28] A meta-analysis[10] found that tuberculosis risk was positively correlated with precipitation, temperature, and humidity. A biological study revealed that a temperature of 37 °C and sufficient oxygen and water are favorable for the propagation of *M. tuberculosis*.[29] Meteorological factors may affect the incidence of tuberculosis by affecting Mtb growth and reproduction of *M. tuberculosis*. An increase in humidity may create a suitable environment for the growth and reproduction of *M. tuberculosis*. However, previous studies have mainly focused on the relationship between meteorological factors, air pollutants, and active tuberculosis not LTBI. Our research findings fill this gap by exploring the impact of meteorological and air pollutants on LTBI. This will broaden the theoretical basis for the prevention and control of LTBI.

Additionally, our study found that vitamin D could reduce the risk of LTBI. Some studies[30,31] have found that a decrease in serum 25-hydroxyvitamin D (25[OH]D) levels can weaken the immune system, making it more difficult for the body to defend itself against *M. tuberculosis* infection. Serum 25D levels affect the progression of latent TB to active disease. Similarly, it is possible that some beneficial effects of vitamin D on TB stem from the suppression of localized inflammatory tissue damage via immunosuppressive Tregs.[32,33] The association between a history of allergies and LTBI has not been proven. However, a randomized controlled trial[34] found that a uniform positive association between TB and all allergic disease outcomes, including eczema, on skin examinations. We also observed a strong association between coal-based biofuels and the LTBI. Prolonged exposure to pollutants released by solid fuels can impair normal clearance of secretions from the mucosal surfaces of the trachea and bronchus. A cross-sectional study found that the use of solid fuels is significantly associated with active TB.[35]

Our study has the following limitations: first, the study population was college students, so it needs to be verified in a wider population; second, PPD testing is influenced by the BCG vaccine, resulting in a certain degree of false positives, which may overestimate the situation of LTBI. However, this study is still innovative in that 1. This is the first study to explore the association between meteorological factors, air pollutants, and LTBI in college students; 2. Participants came from central and western China with good representativeness; 3. The results of this study provide a theoretical basis for prevention and treatment of LTBI in China.

Conclusions

Higher outdoor PM_{10} concentration, history of allergies, and use of coal-based fuels were positively correlated with the occurrence of LTBI. Vitamin D supplementation might reduce the risk of LTBI. Besides, older people were more likely to contribute to strong positive results.

Data Sharing Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

Studies involving human participants were reviewed and approved by the Ethics Committee of Nanjing Municipal Center for Disease Control and Prevention. Written informed consent to participate in this study was obtained from all participants. Data analyses were performed anonymously using unique study numbers.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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