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Original Article

Influential Factors of Tuberculosis Notification Rates in Turkey: A Provincial-Level Spatial Analysis

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Abstract

OBJECTIVE: The total annual count of reported tuberculosis (TB) cases continues to decline throughout Turkey. Recognizing the regions with high and low burdens and revealing the factors affecting TB notification rates may play a role in guiding national control programs. This study aimed to analyze the spatial distribution of TB notification rates from 2005 to 2018 and evaluate the factors contributing to TB rates.

MATERIAL AND METHODS: In this ecological study, we used freely available open data from the Internet. We employed global and local spatial autocorrelation analysis to identify the spatial distribution and the clusters with low and high burdens. We conducted an ordinary least square regression model, spatial lag model, and spatial error model. The best-fitting model was selected via model parameters.

RESULTS: Throughout the study period, the provinces in West Marmara Region (Edirne, Kırklareli, Tekirdağ, Çanakkale) were consistently in a high-burden cluster. In univariate ordinary least square regression, population density, the proportion of contacts screened for TB, the proportion of TB contacts who received prophylaxis, TB dispensary count, mean particulate matter 10 levels, and gross domestic product were found to be positively associated with TB notification rate. The best-fitting multivariate spatial lag model revealed that the proportion of contacts screened for TB (β, *z*-value: 0.89, 2.21) positively affected TB notification rate.

CONCLUSION: The high TB burden in West Marmara Region should warn policymakers to maintain a focused approach to controlling TB in this area. This study showed the importance of contact tracing efforts to prevent the underdetection of TB cases.

KEYWORDS: Tuberculosis, Turkey, spatial analysis, epidemiology, contact tracing
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INTRODUCTION

Mycobacterium tuberculosis is primarily a pulmonary pathogen, but it can infect nearly any part of the body, including lymph nodes, kidneys, bones, and joints.[1] Although one-fourth of the world's population is estimated to be infected with tuberculosis (TB) bacillus, active TB disease develops in 5%-15% of these people.[2] The progression to active TB disease depends on the immune system's response to the bacillus. Risk factors that compromise the immune system, such as human immunodeficiency virus (HIV), immunosuppressive drugs, and diabetes, may precipitate active disease.[3]

According to the World Health Organization (WHO) Global TB Report 2022, it has been stated that 1.6 million people died from TB, and 10.6 million people had TB in 2021, with 98% of these cases originating from low- and middle-income countries.[4] National TB incidences are strongly associated with social and economic determinants,[5,6] driven by global socioeconomic inequalities, population mobility, urbanization, immigration, and population growth. These factors exacerbate malnutrition, inadequate housing, limited access to health care, and food insecurity.[7] Effective TB control necessitates comprehensive social and economic policies, targeting poverty reduction, improved living conditions, and addressing health and socioeconomic issues, particularly among immigrants.

Turkey has committed to reducing the TB burden by adopting the End TB Strategy and the Sustainable Development Goals in 2014-2015.[8] According to national TB surveillance data, the TB incidence (per 100 000 persons) was reported to have declined from 29.4 in 2005 to 14.1 in 2018.[9] Despite the lowering incidence rates, Turkey remains one of the 18 high-priority TB countries in the WHO European Region.[10] According to national reports, the provincial distribution of TB burden differs.[9] Identification of high-incidence regions and exploration of the spatial relationship between TB rates and demographic and socioeconomic factors will guide the national tuberculosis control programs and contribute to the development of tailored disease control strategies by health administrators and policymakers.

This study aimed to analyze the provincial-level spatial distribution of TB incidence between 2005 and 2018 in Turkey and identify the factors influencing TB notification rate.

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MATERIAL AND METHODS

This ecological study contains open data related to Turkey, which is publicly accessible and freely available via the Internet. Turkey, with a population of approximately 85 million, is a transcontinental country located mainly on Anatolian in West Asia, with a small portion on the Balkan Peninsula in Southeastern Europe. Turkey comprises a total of 81 provinces from among 12 NUTS-1 (Nomenclature of Territorial Units for Statistics) regions. For this study, ethical approval was obtained from the Ethical Committee of Dokuz Eylül University, İzmir, Turkey (No.: 2022/13-13).

Data Sources and Explanation

Provincial-level data sources used in the study include:

1. Tuberculosis data: We obtained the total number of TB cases, the total number of contacts screened for TB, the total number of TB contacts who received prophylaxis, and TB dispensary counts from the Health General Directorate of Public Health Tuberculosis Department's TB War reports covering the years 2007-2020. Due to a 2-year lag in data reporting, we analyzed data from 2005 to 2018.
2. Population and socioeconomic data: Data on population, population density, gross domestic product (GDP), average household size, the total number of foreign national populations, and foreign national immigrants were sourced from the Turkish Statistical Institute's website (https://data.tuik.gov.tr/).
3. Air quality data: Mean inhalable particulate matter 10 (PM10) levels were obtained from The Union of Chambers of Turkish Engineers and Architects' Air Pollution Report (2018).
4. Income and wealth index: The income and wealth index is a composite measure that accesses people's ability to meet their basic needs and protect themselves against economic and personal risks. It ranges from 0 to 1 and includes 3 key indicators: saving deposits per capita, the proportion of households in the middle and higher income groups, and the proportion of households declaring that they cannot meet their basic needs. Given the historical association between TB and poverty, we incorporated the income and wealth index as a provincial predictor for TB notification rates.
5. Syrian population data: Data on total Syrian population under temporary protection was sourced from Republic of Turkey Ministry of Interior Presidency of Migration Management, Migration Report for the year 2016.
6. Turkey spatial data: Spatial data for Turkey were retrieved from GADM (Database of Global Administrative Areas), version 3.6, available at https://gadm.org/download_country_v3.html.

Data Preparation and Statistical Analysis

Due to the dynamic nature of infectious diseases, there would be a spatial dependency between the geographic neighborhood areas in terms of both disease burden and associated factors.[11] Spatial econometric models have been used to evaluate spillover effects, recognizing that neighboring units share common economic and social infrastructures. The integration of spatial statistics makes it possible to detect disease clusters and allows us to analyze disease occurrence associated with socioeconomic and environmental factors of the geographic units. In this study, we used global and local autocorrelation analyses and estimated univariate and multivariate ordinary least squares (OLS) regression and spatial econometric models.

We calculated TB notification rates by dividing the total number of reported TB cases (including both new and previously treated cases and all the cases regardless of anatomic region) by the provincial population. To investigate the spatial distribution of TB rates, we performed global and local autocorrelation analyses. Initially, we established an 81 × 81 provincial neighborhood matrix based on the queen (a piece in the game of chess) contiguity using Turkey geospatial data. Then, we weighted these provinces according to their neighborhood relationship, creating a weighted neighborhood matrix. To assess the presence of global spatial autocorrelation for each year, we employed the empirical Bayes index modified Moran's *I* permutation test (EBI Moran's *I*).[12] The Moran's *I* statistic allows for the analysis of the spatial dependence of the data. Similar to the correlation coefficient, values range from −1 to +1. Negative values closer to −1 indicate strong negative autocorrelation, suggesting that observation values in adjacent areas are dissimilar. Conversely, values approaching +1 indicate strong positive autocorrelation, suggesting the presence of clustering.

For the local autocorrelation analysis, we identified both cold (low–low) and hot (high–high) clusters in TB incidence using the Getis–Ord *Gi* local spatial autocorrelation method.[13] This method evaluates provinces and their neighbors collectively and calculates *z*-scores for each province. Statistically significant positive *z*-scores ($Z > 1.96$) indicate hot clusters with high TB incidence, while statistically significant negative *z*-scores ($Z < -1.96$) denote cold clusters with lower TB incidence.

In regression analysis, we initially conducted univariate and multivariate OLS (linear) regression using provincial TB notification rates from the year 2018 as the dependent variable. The provincial-level explanatory variables were categorized as follows: TB surveillance variables (contacts screened for TB, TB contacts who received prophylaxis, and TB dispensary count), demographic variables (population density,

Main Points

- This study analyzed the spatial distribution of tuberculosis notification rates from 2005 to 2018.
- Provinces in the West Marmara Region (Edirne, Kırklareli, Tekirdağ, Çanakkale) consistently exhibited a high-burden cluster.
- The findings of the multivariate spatial lag model demonstrated a positive association between the proportion of contacts screened for tuberculosis and tuberculosis notification rates.
- The study emphasizes the critical role of contact tracing efforts, particularly for individuals with known exposure to tuberculosis patients.

average household size, foreign nationals, foreign national immigrants, and Syrian population under temporary protection), air quality (mean PM10 levels), and economic variables [gross domestic product (GDP), income and wealth index). We transformed certain variables, including the total number of contacts screened for TB, the total number of TB contacts who received prophylaxis, the total number of foreign national populations, foreign national immigrants, and total Syrian population under temporary protection, into proportions (%) by dividing them by the total provincial population. To ensure the normality, we logarithmically transformed the TB rates, mean PM10 levels, and GDP. Also, multicollinearity among explanatory variables was checked. Model outputs was expressed as β coefficients along with their 95% confidence intervals. To assess the presence of spatial autocorrelation in the residuals from the estimated multivariate OLS model, we employed Moran's *I* test. The detection of spatial autocorrelation in the OLS model residuals shows that there would be unaccounted spatial patterns in the model, and spatial models could be used alternatively to apply unbiased model parameters.

Upon confirming the presence of spatial dependency in the residuals, we proceeded with spatial lag model (SLM) and spatial error model (SEM) to account for this spatial dependency. Spatial lag model is an econometric model used to analyze spatial data when there is evidence of spatial autocorrelation. Spatial lag model introduces a lag variable which represents the weighted average of the dependent variable (TB notification rates) in neighboring provinces accounting for spatial spillover effects. Spatial error model is another spatial econometric model that assumes the spatial autocorrelation arises from an error term rather than a spatially lagged dependent variable. Details of the 2 models can be read more in-depth in the paper by Bivand and Piras.[14] Model outputs was expressed as β coefficients, standard errors (SE), and *z*-values. To select the best-fitting model, we compared model parameters using Bayesian information criterion (BIC) and log-likelihood values. The best model was chosen based on a lower BIC value and a higher log-likelihood. We used R (A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/) version 4.3.1 for data analysis and visualization.

RESULTS

Between 2005 and 2018, Türkiye reported a total of 219 338 cases. The highest number of notified cases was concentrated in İstanbul (n = 69 018, 31.5%), İzmir (n = 10 969, 5%), and Bursa (n = 9745, 4.4%). In contrast, Ardahan (n = 177, 0.08%), Bayburt (n = 128, 0.06%), and Tunceli (n = 86, 0.04%) reported the lowest numbers of cases. Figure 1 illustrates TB notification rates in these provinces by years. Over the 14-year period, provincial-level TB notification rates generally exhibited a decreasing trend with occasional yearly fluctuations.

Table 1 presents the results of the global spatial autocorrelation analysis for the annual TB rates spanning from 2005 to 2018. EBI-Moran's *I* values (median: 0.47, minimum–maximum: 0.43-0.59) were found to be statistically significant (*P* = .001), indicative of positive spatial autocorrelation.

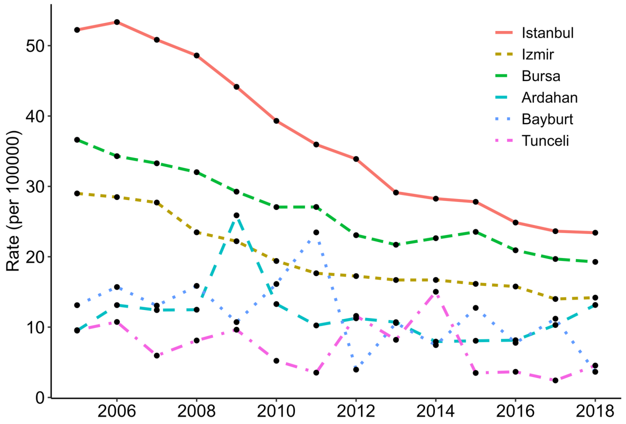

Figure 1. Tuberculosis notification rates (per 100 000) in İstanbul, İzmir, Bursa, Ardahan, Bayburt, and Tunceli (2005-2018).

We conducted local spatial autocorrelation analysis to detect localized patterns in the distribution of TB notification rates. Throughout the study period (2005-2018), the provinces in the West Marmara Region (Edirne, Kırklareli, Tekirdağ, Çanakkale) and Kocaeli were consistently exhibited in high–high clusters. İstanbul was part of a high–high cluster in all years except 2016, and Bursa was in a high–high cluster for 8 years out of 14 years (*P* < 0.05). Although low–low burden clusters were not stable over time, they were generally formed covering Western Anatolia (Ankara, Konya, Karaman), Central Anatolia (Kırıkkale, Aksaray, Niğde, Nevşehir, Kırşehir, Kayseri), and Mediterranean region (Antalya, Isparta, Burdur) provinces in most of the period. In 2018, a high–high cluster included Edirne, Kırklareli, Tekirdağ, Çanakkale, Balıkesir, Bursa, İstanbul, Kocaeli, Sakarya, Düzce, Zonguldak, and

Table 1. Global Spatial Autocorreleation Analysis Results for Tuberculosis Notification Rates in Turkey from 2005 to 2018

Year	Empirical Bayes Index Moran's *I*	*P*
2005	0.44	.001
2006	0.44	.001
2007	0.51	.001
2008	0.59	.001
2009	0.49	.001
2010	0.45	.001
2011	0.47	.001
2012	0.48	.001
2013	0.43	.001
2014	0.51	.001
2015	0.49	.001
2016	0.44	.001
2017	0.43	.001
2018	0.46	.001

Bartın provinces, while a cold cluster were detected including Van, Şırnak, and Siirt (Figure 2).

With the provincial-level variables, we initially conducted univariate and multivariate OLS regression (Table 2). In univariate analysis; TB surveillance variables [proportion of contacts screened for TB (β, 95% CI: 1.42, 0.56- 2.27), proportion of TB contacts who received prophylaxis (β, 95% CI: 7.29, 2.58-12.00), and TB dispensary count (β, 95% CI: 0.04, 0.01-0.06)], population density (β, 95% CI: 0.40, 0.10-0.70), GDP (β, 95% CI: 0.30, 0.02-0.58), and mean PM10 levels (β, 95% CI: 0.25, 0.03-0.47) were found to be positively associated with TB notification rates. In the multivariate analysis, only the proportion of contacts screened for TB retained statistical significance (β, 95% CI: 1.03, 0.09-1.97). Moran's *I* test on the residuals of the multivariate regression model indicated a significant positive spatial autocorrelation in the residuals (Moran *I* statistic standard deviate: 2.80, $P = .003$).

After observing the presence of spatial autocorrelation, we employed both SLM and SEM with all explanatory variables (Table 3). Spatial lag model (BIC: 120.5, log-likelihood: −29.5) demonstrated a better fit compared to SEM (BIC: 123.2, log-likelihood: −30.9). Spatial lag model revealed a spatial lag coefficient of 0.43 (*z*-value: 3.5, $P < 0.0001$) indicating the presence of spatial dependence whereas SEM suggested the existence of a spatially correlated error structure (lambda : 0.47, $P < 0.001$). In the SLM, contacts screened for TB (%) was positively associated with a TB notification rate (β: 0.89, SE: 0.40). However, in SEM, no significant provincial-level variables were found.

DISCUSSION

Tuberculosis surveillance has been one of the meticulously implemented and systematically reported infectious disease surveillance programs in Turkey. Reporting of TB cases is mandatory in Turkey. Prior to 2005, TB department was receiving aggregated data calculated monthly by TB dispensaries. In 2006, with the introduction of the Directly Observed Treatment Strategy (DOTS), individual data collection was initiated, enhancing the data quality. This study period spans from 2005 to 2018, during which significant improvements in data quality occurred with the introduction of the DOTS in 2006.

This study revealed disparities in TB rates across Turkey, with a notable aggregation of high TB burden observed in the West Marmara Region provinces (Edirne, Kırklareli, Tekirdağ, Çanakkale), Kocaeli, and İstanbul. A systematic review of 79 geospatial studies found that 39% of them reported high-burden spots associated with poor socioeconomic conditions.[15] However, this situation may not align with Turkey's context, as West Marmara Region provinces boast relatively high economic status, ranking in the top 25 in GDP and within the top 50 according to the income and wealth index. The high TB burden in these regions may be attributable to their healthcare and surveillance capacity. As a densely populated metropolitan city, İstanbul offers extensive diagnostic and

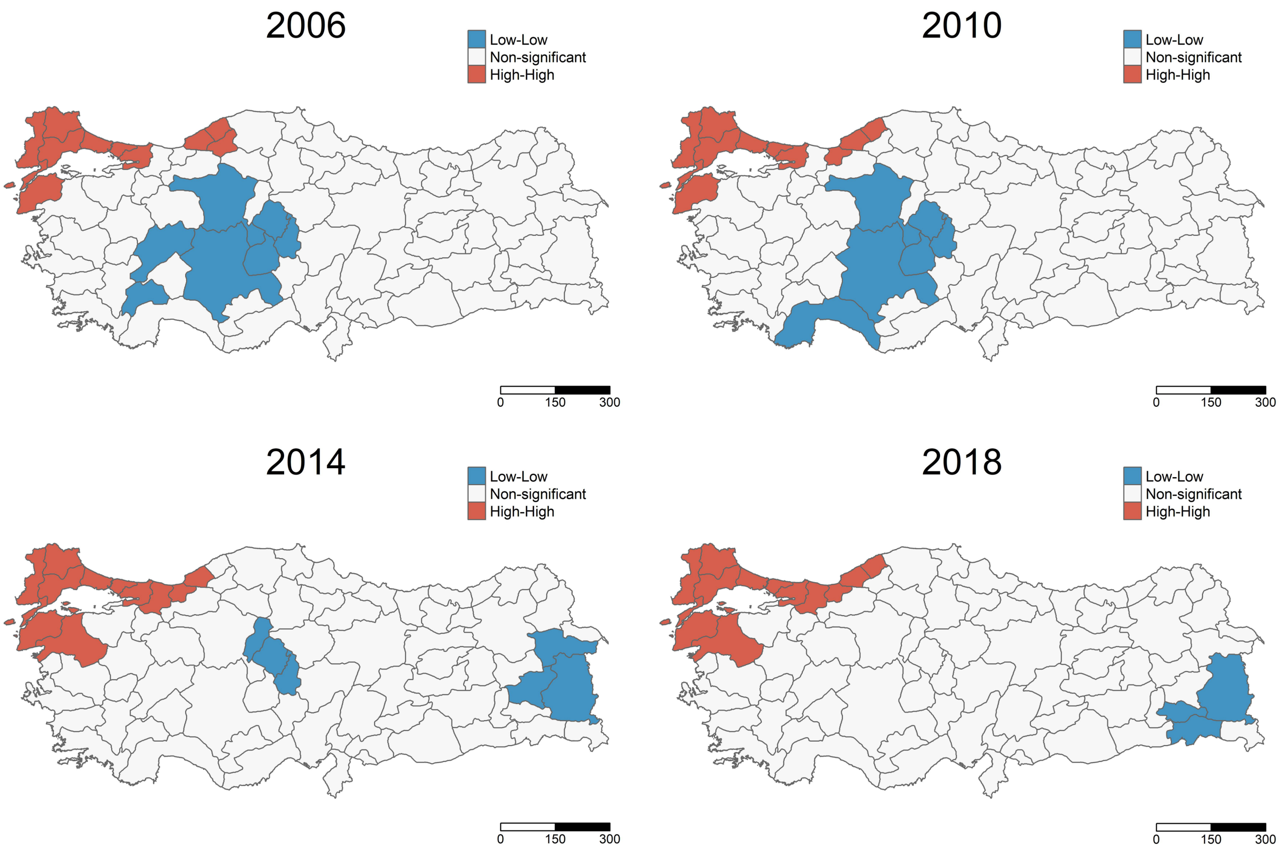

Figure 2. Local autocorrelation analysis of tuberculosis notification rates in Turkey for the years 2006, 2010, 2014, and 2018. Provinces in red indicate high incidence clusters while those in blue colors indicate low incidence clusters. White areas represent nonsignificant aggregations.

Table 2. Results of Univariate and Multivariate Ordinary Least Squares Regression for the Factors Effecting Tuberculosis Notification Rate at Provincial Level in Turkey, 2018

	Ordinary Least Regression			
	Univariate		**Multivariate**	
	β	**95% CI**	β	**95% CI**
TB surveillance variables				
Contacts screened for TB (%)	1.42	0.56-2.27*	1.03	0.09-1.97*
Contacts who received prophylaxis (%)	7.29	2.58-12.00*	2.49	−2.90 to 7.88
TB dispensary count	0.04	0.01-0.06*	0.004	−0.07 to 0.08
Demographic variables				
Population density (per 1000 km^2)	0.40	0.10-0.70*	0.19	−0.64 to 1.03
Average household size	−0.09	−0.21 to 0.03	−0.12	−0.31 to 0.08
Foreign nationals (%)	−0.00	−0.11 to 0.10	−0.27	−0.76 to 0.23
Foreign national immigrants (%)	0.05	−0.22 to 0.31	0.63	−0.55 to 1.82
Syrian population under temporary protection (%)	0.004	−0.005 to 0.01	0.004	−0.005 to 0.01
Economic variables				
Gross domestic product (log)	0.30	0.02-0.58*	0.18	−0.32 to 0.68
Income and wealth index	0.46	−0.09 to 1.02	-0.47	−1.64 to 0.71
Air quality				
Mean PM10 levels (log)	0.25	0.03-0.47*	0.16	−0.09 to 4.40

Multivariate ordinary least squares model parameters: BIC : 125.2; log-likelihood: −34.04.
*$P < 0.05$.

Table 3. Results of Spatial Lag Model and Spatial Error Model for the Factors Effecting Tuberculosis Notification Rate at Provincial Level in Turkey, 2018

	Spatial Lag Model			**Spatial Error Model**		
	β	**SE**	***z*-Value**	β	**SE**	***z*-Value**
Model intercept	1.43	1.98	0.72	2.99	2.18	1.37
TB surveillance variables						
Contacts screened for TB (%)	0.89	0.40	2.21*	0.71	0.39	1.82
Contacts who received prophylaxis (%)	1.55	2.32	0.67	1.41	2.26	0.62
TB dispensary count	0.02	0.03	0.49	0.01	0.03	0.36
Demographic variables						
Population density (per 1000 km^2)	0.004	0.36	0.01	0.02	0.40	0.04
Average household size	−0.07	0.08	−0.81	−0.07	0.10	−0.68
Foreign nationals (%)	−0.18	0.21	−0.83	−0.12	0.20	−0.63
Foreign national immigrants (%)	0.47	0.51	0.92	0.36	0.48	0.75
Syrian population under temporary protection (%)	0.003	0.004	0.90	0.003	0.004	0.72
Economic variables						
Gross domestic product (log)	0.08	0.21	0.38	0.12	0.24	0.51
Income and wealth index	−0.37	0.50	−0.74	−0.49	0.53	−0.94
Air quality						
Mean PM10 levels (log)	0.17	0.10	1.67	0.21	0.11	1.89

Spatial lag model parameters: BIC: 120.5, log-likelihood: −29.5; spatial error model parameters: BIC: 123.2, log-likelihood: −30.9.
*$P < 0.05$.

treatment services. Notably, 2 out of 4 of Turkey's largest reference hospitals are located in İstanbul, contributing significantly to TB diagnosis and treatment services. It is also worth emphasizing that Edirne and Kırklareli are border provinces.

Human immunodeficiency virus coinfection has a substantial impact on TB incidence. The Global TB Report 2022 highlighted that the rate of HIV-positive TB cases was on the rise in the European Region.[4] A study by Dye et al[5] investigating TB incidence trends in 134 countries found that the rates were falling more quickly in countries with lower HIV infection rates. Another study from Brazil used spatial analysis to identify high-risk areas for pulmonary TB and found a higher proportion of people living with HIV in high-risk areas compared to low-risk areas.[16] Unfortunately, we had no provincial data on HIV. Therefore, it is crucial to investigate the impact of HIV coinfection on high-burden regions in Turkey in future studies.

In this study, univariate analysis revealed positive associations between TB incidence and TB surveillance variables. However, in the multivariate SLM, only the proportion of contacts screened for TB was a statistically significant determinant of TB incidence. Efficient and reliable surveillance systems are vital for monitoring TB cases. In Turkey, TB dispensaries serve as the primary operational units of the TB Control Programme, responsible for screening, diagnosis, treatment, follow-up, notification, and registration. Contact tracing carried out by the TB dispensaries identifies contacts of the patients and screens them. A local study conducted in the capital city of Turkey demonstrated that the initiation of active surveillance activities led to a substantial increase in new cases.[17] Moreover, notifications may be limited by underascertainment due to not all cases seeking healthcare or by underreporting due to the failure of reporting cases.[18-20] Standardizing and strengthening contact tracing procedures at the provincial level would enhance case finding and thus TB notifications. Targeted interventions, especially in low–low burden regions, such as replacing the personnel shortage and providing an optimal number of TB dispensaries per population, may contribute to better surveillance activities.

Despite the consistent decline in TB notification rates year by year, foreign-born cases are increasing in Turkey.[9] The migration flow to Turkey has increased over the past years due to the Syrian conflict that began in 2011. The total number of Syrians under temporary protection was 2 834 441 in 2016, and has risen to 3 288 755 in 2023.[21] Syrian migrants comprise an increasing proportion of foreign-born TB patients in Turkey.[22] Within the temporary shelters; active screening, referral, physician presumption, and consecutive examination have led to the diagnosis and treatment of a total of 1022 cases of active tuberculosis among Syrian refugees between 2012 and 2015.[23] When comparing the burden of TB between Syria and Turkey, the 2 countries exhibit a similar baseline rate, although this claim is debatable due to Syria's fragmented and disrupted surveillance activities.[23] Additionally, migrants may experience poor and overcrowded living conditions. While our study did not provide spatial evidence of the impact of foreign-born or Syrian populations on TB notification rates, it is essential that control measures continue to focus on foreign-born individuals and immigrants.

Tuberculosis has historically been linked to poverty due to its association with factors such as limited access to health services, delayed diagnosis, living and working in overcrowded and poorly ventilated environments, as well as malnutrition.[7,24] In the study of Janssens and Rieder, a negative correlation was identified between GDP and TB incidence at the country level.[25] However, in our study, we observed a positive association between GDP and TB notification rates, which contradicts the conventional understanding that TB is a disease of the poor. Similarly, in a study by He et al,[26] GDP was found to be positively associated with pulmonary TB rates. They attributed this unexpected finding to internal migration patterns, with individuals from rural areas moving to economically prosperous regions for physical labor opportunities.[26] Given their attractiveness for informal employment, this argument could also be relevant for high GDP areas in Turkey. Moreover, in this study, the association between GDP and TB rate may also be linked to the availability of diagnostic facilities, health-care experience, and a more favorable health system in high GDP regions.

The study has a few limitations. First, the spatial level used in this study (provinces) may remain relatively large for the spatial modeling of TB. Conducting spatial analyses on smaller levels, such as districts within a province, with available data, might yield more precise and reliable results. Nonetheless, this study is the first to analyze spatial distribution in Turkey that provided a valuable overview of the distribution of TB notification rate. More detailed spatial studies on smaller scales are needed with updated data. Secondly, the practical application of this study is not easy because implementing real-life interventions or policies on provincial level would be challenging. Thirdly, while the univariate analysis showed an association between PM10 levels and TB rates, the reliance on PM10 levels is limited by the fact that 38% of monitoring stations lacked reliable data reception in 2018.[27] Lastly, it is important to note that we were unable to investigate the impact of HIV coinfection and immunosuppression factors, such as malignancy and the use of immunosuppressive drugs, due to the unavailability of provincial-level data on these variables.

In conclusion, this study underscores the importance of contact tracing efforts, particularly among individuals with known exposure to TB. While implementing such provincial-level measures may present challenges, it is imperative for policymakers to adopt a targeted approach in TB control programs that takes into account regional variations in TB incidence.

Ethics Committee Approval: This study was approved by Ethics Committee of Dokuz Eylül University (Approval number: 2022/13-13, Date: 2022).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.N.E.; Design – A.N.E.; Analysis and/or Interpretation – A.N.E.; Literature Review – A.N.E., P.K., D.Ç.; Supervision – P.K., D.Ç.; Data Collection and/or Processing – P.K., D.Ç.; Writing – A.N.E., P.K., D.Ç.; Critical Review – A.N.E., D.Ç.; P.K.

Declaration of Interests: The authors have no conflicts of interest to declare.

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