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Short Communication

Association of ambient temperature with tuberculosis incidence in Japan: An ecological study

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ABSTRACT

Objectives: Although several studies have investigated the effects of temperature on the incidence of tuberculosis (TB) in a single city or region, few studies have investigated the variations in this association using nationwide data. This study aimed to quantify the association between temporal variations in TB incidence and temperature across Japan.
Methods: The data on the weekly number of newly confirmed TB cases and meteorological variables in 47 Japanese prefectures from 2007 to 2019 were collected. The exposure-response relationships between TB incidence and temperature were quantified using a distributed lag nonlinear model for each prefecture, and estimates from all prefectures were then pooled using a meta-regression model to derive nationwide average associations.
Results: This study included 335,060 patients with TB. Compared to those with minimum risk temperature on TB incidence (10th percentile at 4.45°C), people who were exposed to the highest temperature concentrations had a 52.0% (relative risk 1.52, 95% confidence interval 1.04-2.23) higher risk for TB incidence at the 99th percentile (30.1°C). Our results also emphasized the heterogeneity of these associations in different prefectures. *Conclusions:* Strengthening monitoring and public health strategies aimed at controlling temperature-related TB may be more effective when tailored to region-specific meteorological conditions.

Introduction

Tuberculosis (TB) remains a major global public health problem; it was estimated that 10.6 million people fell ill due to TB in the year 2022 [1]. In Japan, a medium-burden TB country, there were 11,519 newly confirmed TB cases according to the Japan TB Surveillance Center's "Annual Report 2022" [2]. Seasonal variations in the incidence of TB have been widely assumed. For instance, a systematic review reported that in the majority of studies (82.4%, 49/57), the incidence of TB peaked in spring or summer and decreased in late autumn or winter (e.g. the United States of America and the United Kingdom) [3]. However, to date, no large-scale or national studies in Japan have examined the association between TB incidence and mean temperature while adjusting for mutually confounding seasonal factors. Indeed, to achieve the global goal of TB elimination, priorities for key control measures and target populations should be determined on the basis of scientific evidence in each country and region, including Japan. This study aimed to elucidate the effect of ambient outdoor temperatures on TB incidence across Japan over a study period of 13 years (from 2007 to 2019).

Methods

We obtained national surveillance data on the weekly counts of newly confirmed TB cases reported between 2007 and 2019 across all 47 Japanese prefectures from the Infectious Disease Weekly Report, sourced from the National Epidemiological Surveillance of Infectious Diseases data under the Ministry of Health, Labour and Welfare, Japan [4]. TB is defined by a combination of clinical symptoms (e.g. cough, sputum, fever, and chest pain) and laboratory tests (positive sputum smear examinations for acid-fast bacilli, isolation of *Mycobacterium tuberculosis* complex by culture, detection of *M. tuberculosis* complex by nucleic acid testing, tuberculin skin tests, interferon-γ release assays, chest radiographs, or clinical decision). All medical institutions and public health centers report TB infections through the notification of patients with TB. Daily ambient meteorological variables, such as the mean temperature (°C), minimum and maximum temperature (°C), and relative humidity (%) measured at a single monitoring station in the capital city of each prefecture were used according to the Automated Meteorological Data Acquisition System [5]. The diurnal temperature range (DTR) was calculated as the difference between the daily maximum and minimum temperatures. For each variable, we computed the average weekly value for the corresponding week from 2007 to 2019 for each prefecture.

We conducted a two-stage meta-analysis to investigate the association between temperature and TB incidence at the country level [6].

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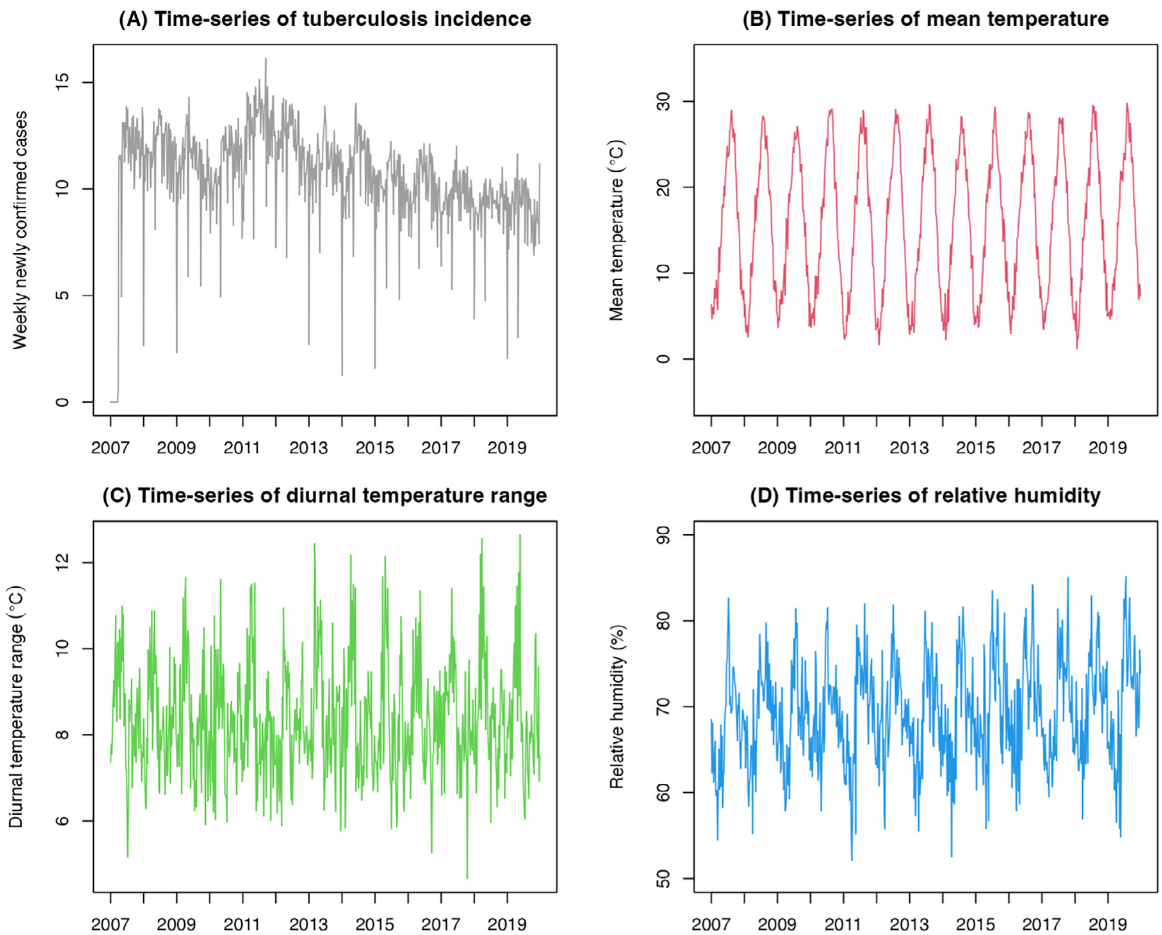

Figure 1. Time-series of tuberculosis incidence and meteorological variables in Japan. Weekly time series of (a) newly confirmed tuberculosis cases, (b) mean temperature in°C, (c) diurnal temperature range in°C, and (d) relative humidity in % for each prefecture averaged for the entire country from 2007 to 2019.

Note that this study is regarded as a type of ecological study in causal inference. All modeling and statistical computations were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) with the R packages "dlnm" and "mixmeta." In the first stage, we used a generalized linear model with a quasi-Poisson distribution and logarithmic link function to estimate the association between the mean temperature and TB incidence in each prefecture. To describe nonlinear and delayed associations, we modeled the cross-basis function with a natural cubic B-spline (NCS) function for mean temperature with three internal knots equally spaced at the 25th, 50th, and 75th percentiles of the prefecture-specific distributions. Based on the previous literature, we initially examined lag periods of up to 26 weeks for the mean temperature using an NCS function with three internal knots placed at equal distances on a log scale [7]. Furthermore, we included the NCS of the week number for each year with four degrees of freedom (df) and the NCS of the year number with three df to control for seasonality and long-term trends. We also incorporated the autoregressive term of weekly counts at lags of 1 and 2 weeks to match the transmission mechanism. After obtaining bi-dimensional estimates, we reduced the dimension of the coefficient to be compatible with the meta-analysis in the second-stage model. We defined the minimum risk temperature (MMT) based on the cumulative curves observed across all the prefectures. The minimum risk was determined between the 1st and 99th percentiles of the mean temperature. The MMT percentile (MMTP) was estimated as the percentile of the MMT based on the mean temperature distribution. These MMTs were subsequently recentered using the best linear unbiased predictions (BLUPs), as outlined in the subsequent second-stage modeling. Thereafter, the overall lag-cumulative relative risks (RRs) for cold (1st percentile) and heat (99th percentile) were quantified, with the risk at the MMT serving as the reference point. In the second stage, we applied a mixed-effects meta-analysis to pool the prefecture-specific coefficients obtained in the first stage to obtain nationwide estimates. We included prefecture-specific mean temperature, DTR, and relative humidity as meta-predictors to address the between-prefecture variability, which can be explained by differences in the meteorological conditions. Residual heterogeneity was tested and quantified using a multivariate extension of the Cochran *Q*-test and *I*-square statistic. We derived BLUPs for prefecture-specific estimates from the multivariate model fit. To evaluate the robustness of our results, we performed several sensitivity analyses by altering the df of the adjustment for seasonality (NCS of the week number of each year, df = 4-6) and the lag week period of the mean temperature (lag = 26-52) [7]. Additionally, we fit the models with and without autocorrelation terms. Finally, the analyses were repeated using Fourier (trigonometric) terms up to the 6th or 8th harmonics per year instead of NCS. This study was exempted from ethical approval because the analysis was based on anonymized data.

Results

Between 2007 and 2019, 335,060 newly confirmed TB cases were reported across Japan, and the seasonality of TB was not apparent (Figure 1). Consistent seasonality was observed throughout the research period for mean temperature, DTR, and relative humidity. The range of the weekly meteorological variables was –6.7°C and 32.0°C for mean temperature, 2.1°C and 17.6°C for DTR, and 28.0% and 97.2% for relative humidity, respectively (Supplementary Table 1). We observed that

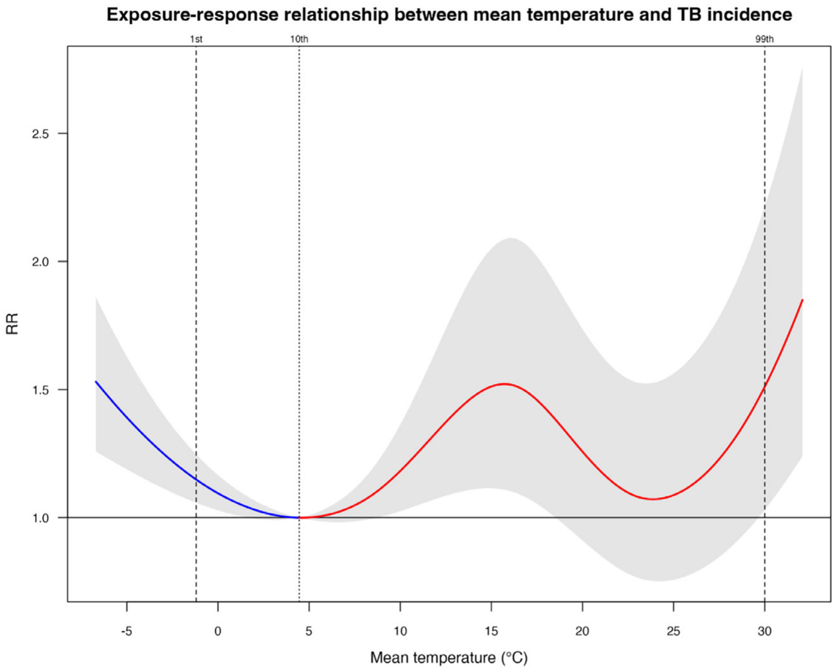

Figure 2. Overall cumulative exposure-response relationship between the mean temperature and TB incidence from 2007 to 2019 in Japan. Exposure-response curve with 95% confidence intervals (shaded region) for ambient temperature (°C) on the number of newly confirmed tuberculosis cases from 2000 to 2019 in Japan. The vertical lines indicate the location for the minimum risk temperature (10^{th}) and RR calculations for cold (1^{st}) or heat (99^{th}).
RR, relative risk; TB, tuberculosis.

the short-term effects of mean temperature on TB incidence showed a nonlinear relationship and the MMTP was identified at the 10^{th} percentile (MMT, 4.45°C) of mean temperature (Figure 2). For instance, a significant heat risk was identified for mean temperature, with an RR of 1.52 (95% confidence interval 1.04-2.23) at the 99^{th} percentile (30.1°C) compared with the MMTP. The RR of 1.03 (95% confidence interval 1.01-1.06) for cold (–1.2 °C) was highest at lag of 0 weeks and decreased thereafter (Supplementary Figure 1). Lagged effects of heat (30.1°C) were found for midterm lags (2-26 weeks). Supplementary Figure 2 presents the exposure-response curves for each prefecture constructed using BLUP. More detailed prefecture-specific exposure-response curves are shown in Supplementary Figure 3. For instance, MMT was identified at the 80^{th} percentile (19.4°C) in Hokkaido, but at the 1^{st} percentile (14.8°C) in Okinawa, suggesting that human adaptability to local climate may vary from prefecture to prefecture. The meta-regression analysis revealed substantial heterogeneity in the association between TB incidence and mean temperature across prefectures (Supplementary Table 2). Sensitivity analyses demonstrated that the association estimates remained generally stable, even when conditions, such as df, lag, autocorrelation, and using Fourier terms were altered, indicating the robustness of the findings (Supplementary Figure 4). However, the association was generally constant across different sensitivity analyses for heat effects, whereas the effects of cold were unstable. Conversely, the analysis using the Fourier term demonstrated a substantial increase in the RR value.

Discussion

This study provides a nationwide assessment of the association between TB incidence and mean temperature in 47 prefectures of Japan over 13 years. We found that the TB incidence increased with extreme heat temperatures. Notably, our results are consistent with those of a recent study in Taiwan that demonstrated a highly significant effect of mean temperature with a 1-month lag on TB trends [8]. In addition, our results were partially consistent with those of a single-city study conducted in Fukuoka, Japan, suggesting the importance of the heat effect [9]. However, several studies have suggested an association between lower mean temperatures and an increased risk of TB incidence in Brazil, Bangladesh, Vietnam, China, and Hong Kong [10]. This discrepancy with the former study might be attributed to different population sizes, local climatic adaptation, effect modification by prefecture-specific characteristics, and differences in statistical model equations. Certainly, some reasons have been considered regarding the causal mechanisms underlying the observed association between mean temperature and TB incidence. One plausible hypothesis posits that during extreme cold or hot weather, individuals spend more time indoors, indirectly influencing contact rates and increasing the likelihood of TB infection. Indeed, it is supported that the environmental conditions of crowded indoor spaces may provide favorable conditions for the survival and transmission of TB [11]. Furthermore, substantial fluctuations in temperature can induce hyperreactivity of the nasal mucosa and epithelial shedding [12]. This triggers an inflammatory response characterized by the recruitment and activation of eosinophils, potentially resulting in respiratory symptoms. Nevertheless, our results demonstrate the importance of mean temperature in TB incidence. This study has several limitations. First, it should be noted that the study used fixed knots at the specific percentiles, which may have resulted in a lack of model fit. Second, we observed variations in exposure-response curves between prefectures, but the specific reasons for these differences remain unclear. Future research should also investigate the factors (e.g. longitude, latitude, and socio-economic status) contributing to these heterogeneities. Finally, to further elucidate the relationship between climate variability and transmission dynamics of TB, future studies should evaluate exposure-response curves using relative humidity as the primary exposure factor alongside mean temperature.

Declarations of competing interest

The author has no competing interests to declare.

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ing of the manuscript. The author has full access to all data in the study and has the final responsibility of submitting it for publication.

Ethical approval

This is not applicable because we used only published data and did not use any personal information. The authors (s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author contributions

KW designed the study, collected and analyzed the data, and drafted the manuscript.

Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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