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Original Research

Natural and Socioeconomic Conditions Influence Tick-Borne Encephalitis Cases in Russia

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Abstract

Tick-Borne Encephalitis (TBE) is an important epidemic disease in the northern hemisphere, especially in Russia which has the longest history of suffering from the disease. In this study, logistic regression model is established combining both nature environment and socioeconomic factors to explore their impact on TBE incidence level. We found that education index, LPI (largest patch area explore index), urban land area, NDVI (normalized difference vegetation index), TBE incidence in the previous year acted as the promoting factors for increasing TBE incidence, whereas annual minimum temperature and social welfare represented by life expectancy years acted as hindering factors. The promoting risk of education index, LPI index, urban land area, NDVI, TBE incidence in the previous year decreased as time went by, but hindering factors, like social welfare, annual minimum temperature, were not observed significant change. Overall, among natural environment factors, urban land area and followed by forest fragmentation greatly affected the presence and the degree of TBE incidence, while among social economic factors, education index played significant roles. The incidence in the previous year also impacted the occurrence and the level of the TBE in most regressions. Attention should be paid on the forest fragmentation level on TBE control, and the incidence of previous years can be used as an indicator for TBE early warning.

Keywords: Tick-Borne Encephalitis; epidemiology; logistic regression; urban expansion; fragmentation

Introduction

Tick-Borne Encephalitis (TBE) is a natural focal viral disease, which is mainly transmitted by *Ixodes persulcatus* and *I. ricinus* [1, 2], can cause human long-term neurological sequelae, fever, and even general intoxication [3]. Tick-borne encephalitis viruses (TBEV) were first found in Russia Far East in 1937 [1], and the incidence and geographic range of TBE have increased in Europe over the past decades [3]. Human TBE incidences were also found in the northern boreal forests of Mongolia [4], and cluster infections in Northeast China [5] and other regions. However, globally, TBEV are chiefly distributed in Russia [2].

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The incidence rates of TBE were affected by comprehensive influence of multiple factors. Climate conditions are important factors influencing the transmission of TBEV. They not only affect the reproduction and survival of ticks and their hosts, transmission of viruses, but also human outdoor activities [6-8]. The increase in TBE incidence rates was reported by resulting from warming winter and early spring [8, 9]. Rapidly warming spring after the cold winter [6] and the extension of vegetable growing season [8] could enlarge the range and time of ticks' activities [10], and promote the prevalence of ticks and TBE. There were different correlations between incidence rates and lowest winter temperature in previous study [8]. Medium cold days (from -10 to -7ºC) had a positive correlation with TBE incidence, while on the contrary, very cold days (<-10ºC) might protect underground ticks [11] and had a negative coefficient. Ticks tend to live in highly humid environment [6]. Studies proved that precipitation, relative humidity [5], and air saturation deficit [12] characterizing the degree of water loss in the environment could affect tick mortality [11]. Except for seasonal temperature change above [8], short-term (daily) temperature and perception showed a positive relationship with incidence rates [13]. Whereas, some other studies have concluded the opposite correlations [5, 7] or no effect was found [14]. In terms of long-term climate variability, an 8-years TBE incidence change was observed in Europe, and the inter-annual fluctuation was possibly related to the North Atlantic Oscillation [15].

Transmission of TBEV is also restricted by topographic factors and vegetation factors. Some studies found that altitude limited the range of ticks' hosts and was negatively correlated with tick bites and TBE incidence rates [5, 16]. The majority number of important tick parasites, such as *Ixodes persulcatus*, inhabits in forest, and thus forest area affects TBE incidences indirectly [9], which were proved to have positive correlations with the coverage ratios of three forest types, broad-leaved forest, mixed forest, and coniferous forest [17]. With the expansion of broad-leaved forest, risk of contracting TBE rose to 70% compared with no-cases countries in mainland China [5]. Researchers found that enhancement in the field area ratio [9] and landscape fragmentation index [17] implied greater biodiversity and biological density at the habitat edge, thereby increased the incidence rates. At the national scale, NDVI was proved to be positively correlated with tick survival [18] and nymphal ticks' abundance [19], and lead to a positive correlation with TBE incidence [20, 21], but the effect of NDVI on tick activity varied from country to country, and some uncorrelated studies had also been observed [22]. As cities continued to expand to suburbs and ticks invaded urban parks and green spaces, cities had gradually become the new focus of TBE infection [2]. At the urban scale, increased NDVI in urban green space in late spring caused a decrease in TBE incidence [12].

In addition, roe deer [17, 21], European hares [9], shore voles (*Myodes glareolus*) [6] and other small rodents were reported to serve as hosts for ticks [24], implying that the densities of these species had an important positive impact on TBE incidence. On the other hand, their densities also had a strong correlation with landscape pattern, which might explain the mechanism of landscape fragmentation index on incidence rates.

From the perspective of exposure, people's lifestyles, such as entertainment [25], berry and mushroom collection [6], income level [26], education level [26] and other factors worked together to influence the frequency human exposed to ticks, personal precautions, and vaccination level, and thus lead to varied TBE incidences. Vaccination primarily protected people who seldom visit forest, because most forest workers had been vaccinated or had acquired protective immunity in Russia [10]. People over the age of 50 were thought to have more active lifestyles and weaker immune function in International Scientific Working Group on Tick-borne encephalitis, making them at increased risk and consequences of TBEV infection [23]. Some studies suggest that there was nearly no relationship between income level and TBE incidence rates [15, 27], but rather an increase in material well-being, for example, the availability of automobiles and transportation infrastructure, could affect the rate of migration from urban to rural areas [15], and thus increased potential opportunities for humans to approach natural risk areas [10].

A large number studies had analyzed the factors affecting TBE incidence rates from the micro-scale (urban scale) to the meso-scale (Europe, China, etc.), and to the large scale (Arctic region). These studies mainly considered survival and reproduction activities of ticks and hosts which transmit TBEV, as well as the role of human activities, including direct or indirect influence of socio-economic and natural factors. Although there were studies building models to discuss how climate change led to human economic loss, our models focused on its influence on human health [28, 29]. In Russia, existing studies had documented the temporal and spatial changes of TBE incidence, incidence rates differences in occupation and age, and climate and ecological factors affecting tick activity [1, 2]. In terms of the risk factors, they only examined the effect of urban expansion on increased TBE incidence in children [1, 2]. Nevertheless, the influence of other socioeconomic factors as well as environmental factors had not been taken into consideration for TBE incidence.

This study combined various types of socioeconomic and natural factors, and built logistic regression models to recognize the key factors that might affect TBE incidence rates, to investigate the mechanism of how climate, land use and multifarious socioeconomic factors influenced TBE incidence rates, and thus to provide a scientific basis for identifying the transmission conditions of natural focal diseases, and offer a reference for the prevention and control of TBE in Russia.

Statistical Analyses

Data and Sources

TBE incidence rates was related to climate that had an interannual periodicity, which was synchronized with the 11-year (10-12-year wavelet scale) change cycle of total solar radiation in Sonechkin D M's study [30]. Urbanization degree also affected the current TBE epidemiological situation. According to the data of the Russian Statistical Service, Russia experienced a rapid urban expansion from 2000 to 2010, and the urban area ratio raised slowly after 2010. Larger selection data gap can clearly compare the reasons for the prevalence of TBE in different stages. Moreover, incidence rates data [1] showed that the incidence rate decreased with the increase of years, and selecting 12 years as the time interval can representatively reflect the above trends. Therefore, considering the availability of dependent variable data and reasons mentioned above, we selected the years 2000, 2012, and 2013 as study years, and extracted TBE incidence data in previous year as a judgment of incidence lag, namely the years 1999, 2011, and 2012.

Table 1. TBE incidence rate ranking standards [1] (Unit: morbidity per 100000).

Ranking	TBE incidence rate range
0	0
1	0-1
2	1-5
3	5-15
4	>15

TBE ranking incidence rates data derived from Malkhazova et al. [1], representing the severity of the incidence, and the ranking standard is represented in Table 1. In the selected years of 2000, 2012 and 2013, the number of areas with no epidemic was basically stable, with 37, 35, and 37 federal districts respectively (Fig. 1). However, the areas with incidence rates at level 1 and level 2 were increasing. There were 10, 15, and 16 federal districts whose incidence rate was at level 1, and 13, 17, and 20 federal districts were at level 2 in three selected years. It might due to the conversion of high-level districts to low-level districts, and was proved by a sharp decline in the number of federal districts with incidence rate at level 4, which decreased from 8 in 2000 to 1 in 2012 and 2013, and the last district at level 4 was Krasnoyarsk Kray.

Socioeconomic variables included education, economic and social factors. Literacy, education enrollment ratio and education index represented education factors. Literacy represented ratio of uneducated people over 15 years old. Education enrollment ratio meant the proportion of educated people in the region from 7 to 24 years old. Education index combined adult literacy rate and enrollment in education before 2010, but considered from mean years of schooling and expected years of schooling after 2010.

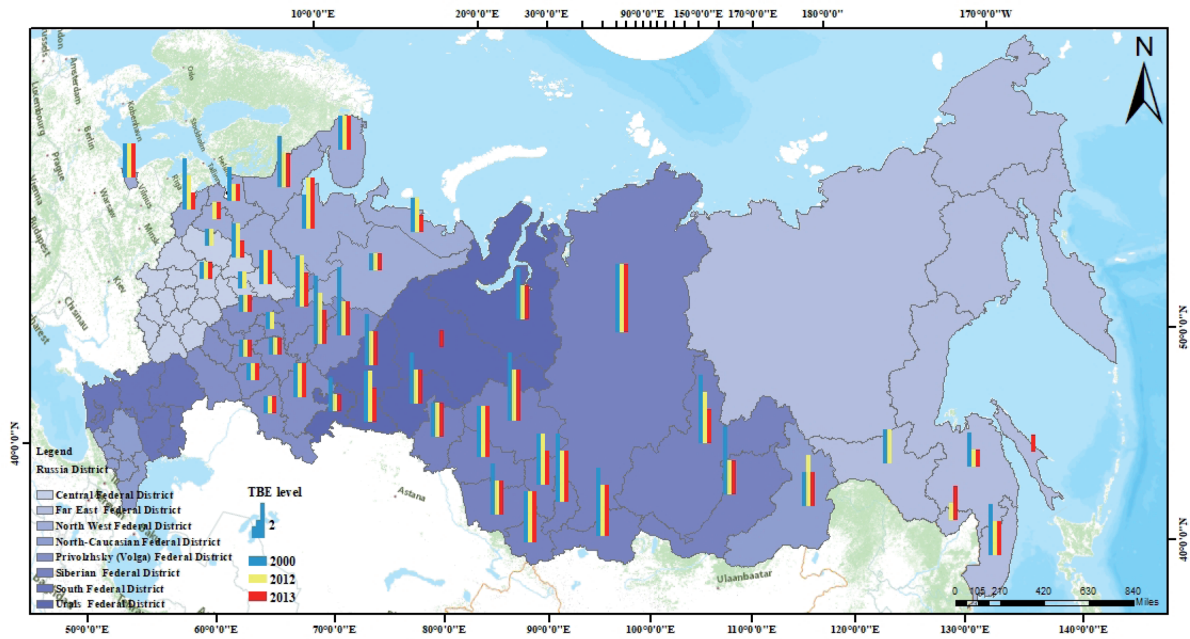

Fig. 1. Distribution of TBE incidence level in Russia.

Income and GDP per capita in PPP (purchasing power parity) were representative index in economic sphere. Social welfare and social development were explained by life expectancy in years, net immigration rate, number of doctors per 100000 people, total population, and unemployment rate. All socioeconomic data were from the Russian federal state statistical service.

Explanation variables in natural sphere were divided into land cover, climate, and landscape index. Land cover indexes included crop land area, urban land area, and maximum NDVI in July and August. Climate factors contained annual average perception and annual temperature (maximum, minimum, average). Landscape indexes consisted of LPI (largest patch area), NP (number of patches), PD (patch density), IJI (interspersion juxtaposition index). NDVI referred to Global 8KM GIMMS Smoothed NDVI Dataset [31]. Climate data were from GHCND (custom global summary of the year) dataset [32]. Land use data were from globe land30 [33]. The base map data of Fig. 1 was from China Online community ENG in ArcGIS online.

Methods

Multiple logistic regression model was used to find out the differences between high grade region and area without cases in factors when TBE incidence rates severity as dependent variable. Firstly, we analyzed the significant variables affecting TBE incidence among all related factors, and performed univariate analysis to find out the influence of related variables on incidence in different years and levels. AIC index was adopted to select independent variables and evaluate the final model. The model with the smallest AIC index was preferentially selected. Combined with the results of literature researches and univariate test, 8 significant factors were finally determined ($P<0.05$).

To further analyze influencing factors, binary logistic regression was established to find out which factor may cause the occurrence of TBE case. Level 1, 2, 3, 4 were combined into one category to compare with level 0, which can more directly reflect the factors affecting TBE cases.

Table 2. Screening significant factors for model (+ indicates significant at $P<0.1$, ++indicates significant at $P<0.05$).

			2000				2012			2013		
Domain	Category	Factors	0-1	0-2	0-3	0-4	0-1	0-2	0-3	0-1	0-2	0-3
Socioeconomic	Education	Education enrollment ratio			++	++						
		Literacy					++	+				
		Education index	+		++	++		+	++			++
	Economic	GDP		++		++	+	+		++		
		Income		++		++						
	Social	Life expectancy in years					++	++	++		++	+
		Net immigration	+						+			
		Number of doctors per 100000 people	++	++	++	++						
		Total population					+					
		Unemployment rate			++	++			++			++
Natural	Land cover	Crop land										
		Urban land		++		++	+			+		
		NDVI		++	++	++	++	++	++	++	++	++
	Climate	PRCP				+			++			
		Taver	++	++	++	++	++	++	++	+	++	++
		Tmax					+	++	+			
		Tmin	++	++	++	++	++	++	++	++	++	++
	Landscape index	IJI	++				+					
		LPI		++	++	++	++	++	++	+	++	++
		NP		+	++	++		++	++	+	++	++
		PD				++						
	Lag	TBElag		++			++	++	++	++	++	++

Land cover data were analyzed using ArcMap 10.2 and calculated to landscapes indexes through Fragstats 4.2. Meteorological station data were converted into regional discrete data by using Kriging interpolation method and Zonal Statistics with the help of Model Builder in ArcMap 10.2. NDVI value of half a month were turned into a quarter using Cell Statistics in Spatial Analyst. Regression analysis were performed on IBM SPSS Statistics 26. Figures were drawing through Origin 2018, ArcMap 10.2, and GraphPad Prism 8.

Results

Preliminary Screening of Impact Factors

The factors collected in this study are of various types and represent strong linearity, and have limited annual sample size (n = 80). Since the data under each category do not follow Gaussian distribution, all variables and incidence rates are performed with non-parametric Mann-Whitney independent bivariate test in order to coordinate the sample size, obtain significant factors, and eliminate the unimportant factors. The analysis between independent variables and TBE incidence severity is shown on Table 2. Considering the availability of factors, and combining with the factors that had a generally significant impact on the incidence rate in the majority of literature, the most representative (with two significant markers) factors were finally selected into the model. The TBE incidence from previous year as a lagged term was included in 2000, 2012, and 2013 models, but not in the overall model. All the variables included in the model passed the multicollinearity test.

The number of factors with significance (P<0.05) in both two domains decreased with years and the number of natural factors with significance (P<0.05) was much larger than that of social factors, indicating that the incidence of TBE was mainly affected by natural factors. The number of socio-economic and natural factors with significance (P<0.05) increased with the increase of TBE incidence rates level in 2000 and 2013, whereas the number of factors in socio-economic domain decreased first and then increased with TBE incidence rates level increase in 2012.

By comparing the number of factors that were significant (P<0.05), factors were selected for the logit regression. The annual minimum and mean temperature were both significant in all comparisons, but based on AIC values, annual minimum temperature (Tmin) (ºC) was included. In addition, NDVI (maximum summer NDVI) representing land cover, LPI (largest forest patch/total forest area) representing landscape were included. Among the socioeconomic factors, education index (EDU) (%) that showed significance on TBE incidence rates at higher levels, life expectancy years (LIFE, in year, representing the general social welfare) with notable effect on incidence rates in 2012 and 2013 were selected. Urban land area (URBAN) (hectare) that has been proven to influence the incidence [2], and with significance in the earlier year in the test was included. Meanwhile, TBE incidence rates ranking data of previous year (TBElag) was also included due to the high frequency of significance in the test.

The Influence of Socioeconomic and Natural Factors on TBE Incidence

Multiple Logistic Regression

The comparisons between case-free (0) and different incidence rates (level 1,2,3,4) in 2000, 2012 and 2013 were shown on Fig. 2. The confidence intervals of all OR values were distributed on one side of 1 in below models, representing that these factors significantly influenced TBE incidences only in one stationary way, that was promoting or hindering.

Annual minimum temperature, GDP per capita, and education index influenced TBE incidence rates in most models in 2000 (Fig. 2). Annual minimum temperature rising was inversely associated with increased risk of TBE incidence rates in 2000. With a 1ºC increase in the annual minimum temperature, the risk of TBE becoming level 1, 2, 3, and 4 decreased by 0.27, 0.254, 0.297, and 0.539, respectively. The higher the year's minimum temperature, the less risk of the region becoming a TBE sever incidence area. On the contrary, the education index led to an increase risk in TBE incidence rates, especially at level 4. For every 1% increase in the education index, the risk of TBE incidence rates becoming level 1, levels 3 and 4 increased by 4.151, 3.45 and 627.435. GDP showed very small contribution to TBE incidence rates for different levels.

LPI index and previous year TBE incidence rates only showed their significance in (0-4) model (Fig. 2d). LPI index had a significant effect only on the risk of becoming level 4. One unit increase in LPI increased the risk of TBE incidence becoming level 4 by 0.447. TBE incidence in the previous year was the main influencing factor that caused high grade incidence (OR = 5630.931, P<0.05).

Although there was little difference between factors that are significant from previous multiple logistic regression and later binary logistic regression, the predominant factors were the same. Binary logistic regression analysis performed on areas with cases and without cases (0-all) found that three factors had a significant impact on the occurrence of TBE (Fig. 2e). For every 1% increase in the education index, the risk of having a TBE case in the region increased by 2.285. GDP was also able to increase the risk of having TBE cases, though the contribution to the risk was very low comparing with other factors. As the only limiting factor affecting TBE incidence rates in this model, for every 1ºC increase in the annual minimum temperature, the probability of the study area becoming a case-

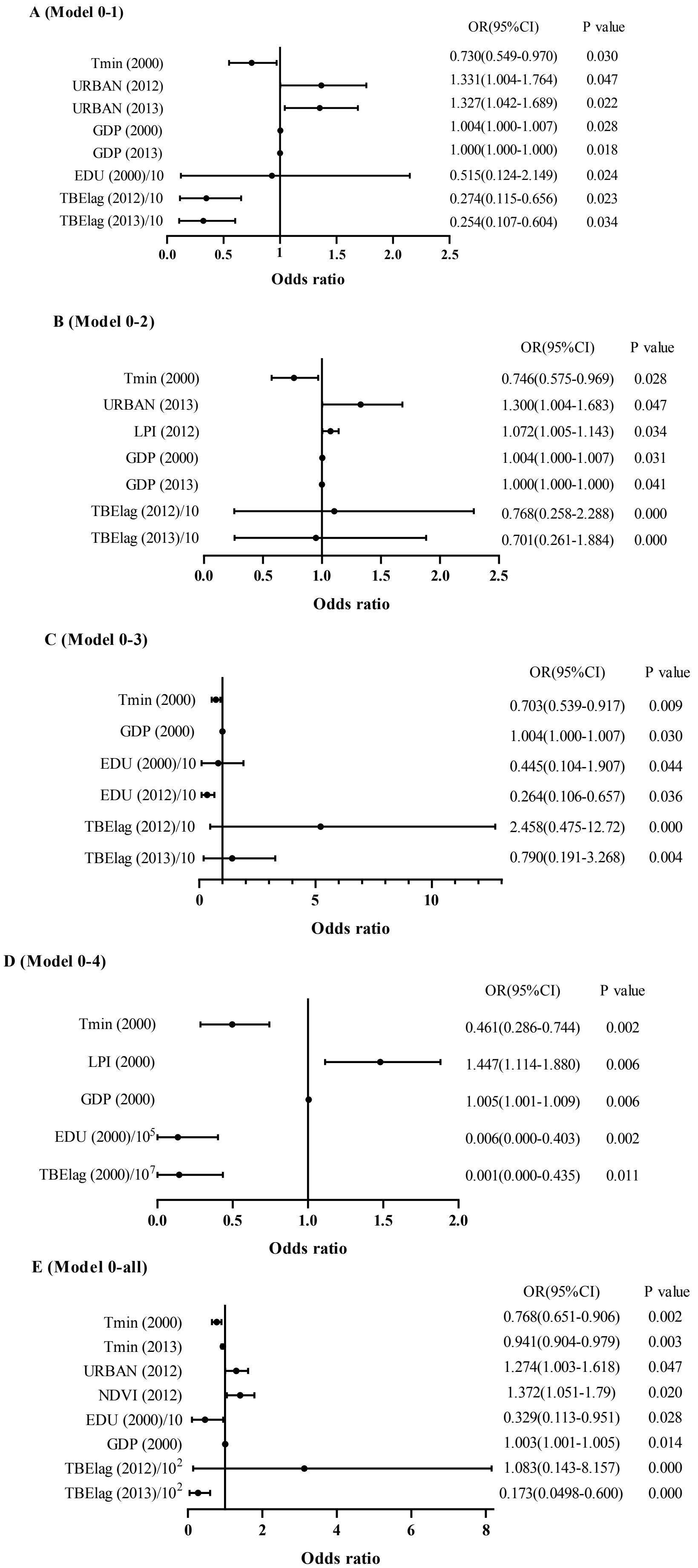

Fig. 2. Forest graphs of logistic regression in different comparisons.

free area increased by 0.768. The presence or absence of TBE cases in the previous year and the LPI index can contribute to higher TBE risks but not link to the incidence occurrence in 2000.

In 2012, urban land area, LPI index, and education index promoted incidence rates only in one model for each regression in multiple logistic regression (Fig. 2). Every 1 hectare increases in urban land area, the risk of TBE incidence rates elevating to level 1 increased by 0.331. For every 1% increase in the education index, the risk of becoming level 3 in-creased by 1.643, which was smaller than that in 2000. When LPI increased by 1 unit, the risk of incidence increasing to level 2 was 0.072, less than the risk to level 4 in 2000. Previous year's TBE incidence rates were the main positive factor affecting incidence rates in 2012, showed its effect in every model. With the increase of the incidence rate in the previous year, the incidence rate in this year going up to level 1 (OR = 2.743, $P<0.05$), level 2 (OR = 7.675, $P<0.05$) and level 3 (OR = 24.581, $P<0.05$), and the higher the level was, the greater the risk was.

According to the binary logistic regression analysis in 2012, (0-all) model was observed to have a significant positive correlation between TBE cases in the previous year and cases in the current year, whereas it was not an important factor in 2000 (Fig. 2e). If the area had a case last year, the chance of having a case this year rose 107.346 times.

Urban land area was a primary natural factor in 2012 combining the results in multivariate analysis. For every 1 hectare of urban land area, the probability of finding a TBE case increased by 0.274. NDVI was an emerging significant natural factor in 2012 regression model, only showed a notable effect in (0-all) model. For every 0.01 unit increase in NDVI, the probability of TBE cases occurring in this area increased by 0.372. Comparing two logistic models, NDVI had a significant positive effect on incidence occurrence in 2012, but did not contribute to high TBE risk. On the contrary, education index and LPI index increased severity of TBE risk, whereas do not link to the incidence occurrence in 2012.

Urban land area was an importance natural factor promoting TBE incidence rates in 2013 (Fig. 2). When the urban land area increased by 1 hectare, the risk of TBE incidence rising to level 1 and level 2 increased by 0.327 and 0.3, respectively, and the risk gradually decreased with the increase of the incidence rate. It was worth noting that urban land area only increased TBE incidence rates in (0-1) model in 2012 (Fig. 2a), indicating that the urban land area had a greater impact when incidence rates was low. Compared with 2012, the contribution of urban land area to increase high TBE risk decreased in 2013.

The incidence rate in to previous year was still the dominant factor influencing the incidence rate for the year 2013. The contribution decreased compared with which in 2012, but the basic trend that the index promoting higher TBE risk remained unchangeable.

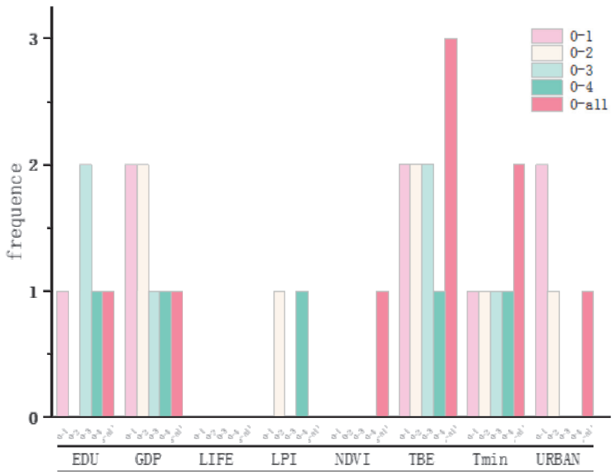

Fig. 3. Frequencies of significance for eight factors in different comparisons.

Comparison between regions with TBE cases and regions without cases (0-all regression) showed that annual minimum temperature and TBE cases in the previous year affected TBE prevalence (Fig. 2e). In 2013, TBE cases in the previous year's contribution was less than in 2012, with a risk value of 17.27. For every 1ºC increase in annual minimum temperature, the risk of finding TBE cases this year decreased by 0.059, much lower than that in 2000.

The frequencies of factors in different comparisons are shown on Fig. 3. TBE incidence in previous year greatly influenced this year's TBE incidence in every comparison and had the largest frequency among all factors. Natural factors, such as annual minimum temperature and urban land ratio, and social economic factors including education index and GDP, were important factors affected TBE incidence. However, urban land ratio tended to associate with low TBE incidence, and other factors nearly showed significance in every comparison.

Table 3 shows the factors may influence TBE severity based on the cases covering all years. Expansion of urban land area promoted high risk of incidence rate in 2012, 2013, and in overall model, while showed no significance in 2000, which implied that urban land area has become an important factor in recent years. An increase of 1 hectare of urban land area increased the risk of TBE incidence to level 1, 2, 3, and 4 by 0.322, 0.229, 0.200, 0.266. This reduction was similar to the 2013 model, indicating that urban land expansion led to low-level TBE incidence, while high-level TBE incidence was less affected by the increase in urban land area.

Annual minimum temperature also affected higher level incidence rates. A 1ºC increase in the lowest temperature throughout the year reduced the risk of becoming a level 4 incidence by 0.088. No significant effect of temperature on the incidence rates level was observed in other comparisons.

Table 3. Logistic Regression Results of TBE Incidence (overall model).

	Variables	OR value (95%CI)	P value
0-all	NDVI	1.212 (1.092-1.346)	0.000
	URBAN	1.263 (1.12-1.424)	0.000
	EDU	1.187 (1.024-1.376)	0.023
	LPI	1.022 (1.003-1.041)	0.026
	LIFE	0.767 (0.667-0.882)	0.000
	GDP	1 (1-1)	0.019
0-1	URBAN	1.322 (1.149-1.521)	0.000
	GDP	1 (1-1)	0.006
	NDVI	1.269 (1.079-1.493)	0.004
	LIFE	0.723 (0.585-0.895)	0.003
0-2	URBAN	1.229 (1.073-1.409)	0.003
	LPI	1.039 (1.015-1.064)	0.001
0-3	URBAN	1.200 (1.021-1.41)	0.027
	EDU	1.436 (1.112-1.854)	0.005
	NDVI	1.261 (1.021-1.557)	0.031
	LIFE	0.713 (0.549-0.927)	0.011
0-4	URBAN	1.266 (1.007-1.592)	0.043
	EDU	1.542 (1.025-2.32)	0.038
	Tmin	0.912 (0.837-0.995)	0.039
	LIFE	0.605 (0.4-0.914)	0.017

LPI index only contributed to the incidence rates risk in (0-2) model. A one-unit increase in the LPI index increased the risk of TBE incidence becoming level 2 by 0.039, and the risk level was less than that in 2012.

Higher TBE incidence rates were mainly affected by education index. For each 1% increase in education index, the risk of TBE incidence rates escalating to levels 3 and 4 are 0.436 and 0.542.

There are two new factors appeared in overall model that affected incidence rates change in multiple logistic regression. The maximum NDVI value in summer had a positive effect on the increase of the incidence rate in relative lower incidence rates level. For 0.01 unit increase of the maximum NDVI value, the risk of incidence rate becoming level 1 and level 3 increased greatly, manifesting that it was the dominant factor that affect lower TBE incidence rates grade. Yet life expectancy years represented a more common function than NDVI, showed its significance in every comparison, indicating a better social welfare can decrease the risk of higher incidence rates.

The results from (0-all) regression were basically consistent with the annual models, except two emerging factors, LPI index and life expectancy years. These two factors affected TBE incidence rates in opposite direction.

NDVI, urban land area, and education index were still the dominant factors affecting the existence of TBE case in different level. Urban land area was the most important factor, for every 1 hectare of urban land area, the probability of having a TBE case increased by 0.263, followed by NDVI and education index, for every 0.01 unit increase in these two factors raised the probability of TBE case existing by 0.212 and 0.187.

Discussion

Generally speaking, the number of TBE case -free areas in three years were basically the same, with 37, 35, and 37 federal districts respectively, but the number of areas at relative low level (level 1 and level 2) increased, and the number of areas at level 4 were becoming less and less, and finally approached 0, indicating that Russia's strict control of the spread and supervision of the TBE epidemic had received some achievement [34].

Natural factors had different effect on TBE incidence rates. The increase of LPI index for the forest accelerated incidence rates risks. The degree of forest patch fragmentation represented the continuity of the ecosystem, and the high degree of which increased biodiversity of ticks and their hosts habitat [9, 17] that could augment hosts number, trigger chain reactions such as an increase in the number of ticks and the rapid spread of viruses between populations, led to an increase in TBE incidence rates. Rapid temperature raising after cold winter could accelerate tick reproduction and activity [6]. Surprisingly, there was a negative correlation between the low winter minimum temperature (<-10ºC) and TBE incidence [8]. It has been studied that low temperature in winter might lead to the death of hibernating ticks. However, the long-term snow cover caused by low temperature can protect the underground ticks [11], so with the increase of the lowest temperature, the snow melted and killed a large number of ticks, as warm spring went by, led to a negative correlation between minimum temperature and incidence. The significant effect of the minimum temperature on the incidence rate mainly appeared in 2000 when the annual minimum temperature was lower than -10ºC in 86.25% of Russia's regions. This result is consistent with Lindgren's [8] study. Temperature factors combined with NDVI can successfully predict transmission and risk of TBE incidence [21]. The highest NDVI in summer was a new positive significant natural factor in overall model and played a major role in increasing incidence. NDVI was closely related to local environmental temperature, humidity, vegetation type and other factors, and was usually analyzed together with temperature into the model, which could well predict the activity and habitat distribution of ticks [36], and improve the prediction effect of the model.

Nymphs were considered to be the main carriers of TBE virus infection in humans [6]. The increase in nymph abundance is related to the increase in NDVI value [19]. The higher the NDVI value, the higher the tick survival rate [18], which directly led to the improvement of disease incidence.

Enlarged urban land area resulted in leveling up incidence rates. Urban expansion not only accelerated land-scape fragmentation, but also made ticks from nearby suburbs invade city parks and green land, increased human exposure to ticks and boosted TBE incidence rates. On one side, the expansion of cities made the current epidemic trend to increase the TBE infections number in urban population [2], moreover, it led to an increase in children's TBE incidence [1]. And the edge of woodland habitat had the most significant activity and the presence of ticks than other green land habitat types in city [35]. Similarly, in the current study, significant positive effect was found mainly for level 1 and 2 in annual models and also for all the levels levels in the overall model. The risk of urban land area improving low-level TBE incidence decreased from 1.331 in 2012 to 1.327 in 2013. In study area, high-epidemic areas had the largest urban land area and the number of forest patches, these factors in non-epidemic areas were lower than that in low-epidemic areas. Incidences may be detected with the largen of urban land in non-epidemic areas, however, due to the limitation of forest patches and poor habitat conditions of ticks, incidence rates only increase to low-level, not to a high level.

Education index was an important factor that caused primary effect on TBE incidence rates. However, unlike the previous study [26], a positive correlation between education index and increasing incidence rates risk was found in current study. The mechanism was complex, on one hand, highly educated people were equipped with abundant personal prevention knowledge, on the other hand, these groups tended to have higher income and stable jobs, prone to have more time and energy to travel towards forest or natural epidemic areas for recreation and thus more likely to be exposed to ticks. In fact, compulsive vaccination in Russia only aimed at teenagers and high-risk people, such as hunters, forest keepers, in high-risk area [37], and vaccination were optional in non-epidemic area. Therefore, the possibility of recreation travelers to get vaccinated before went to forest and epidemic area was low [34].

The risk of education index improving high-level TBE incidence decreased as time went by (Fig. 2), its risk decreased from 4.45 in 2000 to 2.643 in 2012, possibly because the establish of newly supervision organization (Rospotrebnadzor) in the field of human well-being in 2004 [34], vaccinations in place, or general public became better educated, implying that people's awareness of prevention and control has increased, resulting in a reduced influence of education index on promoting incidence rates level.

Life expectancy was an emerging negatively significant socioeconomic factor in overall model. Life expectancy was an important factor that reflected the degree of social welfare, which related to many driving factors, such as health care spending growth, rising living standards, environmental improvements, lifestyle changes and education [38]. Education and skills were major requisites for finding a job, and closely associated with income, which was an important means to achieving higher living standards. However, in this study, education index and life expectancy influenced TBE incidence in two different ways, that might because changing lifestyle was dominant factor when income increasing despite it also led to rising living standards. Unlike material welfare [15], which has a positive effect on incidence rates, the effect of life expectancy on incidence rates not reflected in the increasing contact probability of human and tick, but in better health care conditions. An analysis of studies in the Czech Republic [15] showed that changes in the age structure of the population, such as an aging population, a narrowing of age structure regions, and an increase in the high-risk age group (30-70, about 60) reduced the incidence of TBE. Although GDP (PPP) was included in models, it showed a small proactive effect in incidence risk in the 2000 model while not for other models.

Russian economy and society underwent rapid changes around 2000. With the revision of the regulations in hygiene and epidemiological health, there were some deficiencies in the organization and implementation of immunization, which led to an increase in epidemiological incidence rates and mortality [34]. This might relate to the inconsistent effect of socioeconomic 'factors'.

The TBE incidence level in the previous year has a significant positive impact on current year's incidence level, and the TBE incidence level was mainly affected by the epidemic situation in the previous year. This also indicated that the risks were much higher for the regions already with TBE in the previous years, and the reduction of the annual incidence of TBE was of great significance to the prevention and control of subsequent infectious diseases.

In general, comparing the fitted model for each year and the overall model, the promoting or inhibiting effect of various factors on the incidence rate remains the same. The influence level of urban land area, LPI index, education index, the incidence of TBE in the previous year and other factors that have promoting effects on increasing the incidence rate, decrease with years. Life expectancy years and annual minimum temperature are the hindering factors.

More attention should be paid on urban land area, LPI, and education index to control TBE incidence rates among all factors. We can take TBE incidence level in the previous year as early warning. When it has no case in the previous year, areas which has large urban land area should close monitor their epidemic dynamics, because they may have high risk of becoming low incidence rates level (1 or 2) areas, whereas the incidence rates of areas with higher education index and more discontinuous forest are at high risks of leveling up to 3 or 4, these high-risk areas can get vaccination early. When there were cases in the precious year, risk of TBE incidence broadly expand increase this year, government should take more measures to restrict incidence rates in advance.

Conclusions

We proposed logistic regression models to analyze the influence of related environmental and socioeconomic factors on TBE risk. The models considered six factors affecting TBE incidence and one lagged variable. The results are: 1) The relationships between influencing factors and incidence were different. Education index, LPI, urban land area, NDVI, TBE incidence in the previous year were the promoting factors for increasing TBE incidence, whereas social welfare represented by life expectancy years, annual minimum temperature were the hindering factors. In general, for most of the regressions, urban land expansion leaded to low-level TBE incidence, while high-level TBE incidence was more affected by the increase of education index and LPI. 2) The relative risk of promoting factors decreased with years, especially for education index affecting high-level TBE incidence and urban land area affecting low-level TBE incidence, but no significant inter-annual changes were observed for hindering factors. 3) The number of natural factors with significance was much larger than that of social factors indicating that TBE incidence was mainly affected by natural factors in Russia. 4) Areas with larger urban land area, higher education index, and more discontinuous forest should be paid more attention of emerging TBE incidence, advanced measures, such as vaccination and prevention propaganda, should be taken especially in areas with cases last year and areas have above characteristics. However, long-term climate change could affect the uncertainty of model parameters [39], it is a non-negligible problem in model construction, the next step is to adopt larger data to represent it.

Author Contributions

Conceptualization, LZ and LW.; methodology, LZ and LW.; software, LZ.; validation, LY, HL and LG.; formal analysis, LZ.; investigation, LZ and LW.; resources, LZ.; data curation, LZ and SM.; writing – original draft preparation, LZ.; writing – review and editing, LW.; visualization, LZ.; supervision, LW, LY, HL and LG.; project administration, LY and LW. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

All authors read and approved the final manuscript and have no conflict of interest to declare.

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