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Space-time analysis of human brucellosis considering environmental factors in Iran

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ABSTRACT

Objective: To investigate the associations between the brucellosis and four climatic factors including temperature, precipitation, wind speed and greenness for better understanding the epidemiology of the disease in Iran during April 2009 to March 2012.
Methods: A cross-sectional survey was performed on 39 359 recorded cases during the study period. Pearson's correlation coefficient was used to investigate statistically meaningful temporal and spatial relevance between the disease and parameters. Besides, multiple linear regression was applied to estimate the best combination of the variables for predicting brucellosis incidence.
Results: Pearson's analysis revealed that there are positive temporal correlations between incidence and temperature, wind speed and greenness. Besides, a strong negative temporal association was observed with precipitation. Although a remarkable negative spatial association was observed between aggregated incidence rates and vegetation cover of corresponding counties in winter, this correlation was strongly positive for spring and summer.
Conclusions: The prevalence of brucellosis is considerably affected by climatic conditions. Locations with higher greenness, temperature and wind speed are more susceptible to the disease. In contrast, areas with lower rainfall tend to face surpassing rates. Additionally, greater rates are expected for counties having green springs and summers, with dry winters.

1. Introduction

Brucellosis also recognized as undulant fever, Mediterranean fever or Malta fever is a highly contagious zoonosis. Direct or indirect association with infected livestock and consuming their products, which can contain the brucella for up to 60 days, could lead to invariable transmission of the infection[1]. Except cats that are immune to brucellosis, almost every other domestic animal can be an appropriate host for the causative agents[2]. Numerous health workers are exposed to the disease, since they either neglect the possibility of dealing with a zoonosis or discount the public health implications of the infection[3]. The causative agents *Brucella melitensis*, infecting sheep and goats, *Brucella suis* and *Brucella abortus* which infect swine and cattle respectively create noteworthy financial burdens on the animal owners and cruel human disease[4]. The major agents causing the disease in Iran are *Brucella abortus* and *Brucella melitensis* bacteria[5]. Although this kind of infectious disease has been eradicated from several developed countries, it still appears continually specially in Asia, in particular, Middle East is more volatile[6]. Although the rate of morality for brucellosis is not outstanding, the immune system of human is highly affected by the debility and inconvenience caused as its consequences[7]. The first positive case of human brucellosis in Iran was recognized in 1932 and since then it is considered as an endemic disease in this country. However the first animal vaccination schedule was laid out in 1949, brucellosis is still present as an acute infection in this country[8]. According to the data from the National Commission on Communicable Diseases Control the status of brucellosis in Iran is improving. In 1989 the yearly occurrence exceeded 1 000 patients per million whereas in 2003, the annual incidence had dropped to 238 cases per million[9]. Nevertheless, human brucellosis still remains a considerable burden on this country[10]. Worldwide incidence of human brucellosis disease has been depicted in Figure 1. There is no doubt that the critical situation of Iran among most of other countries is troubling.

There is a wide range of factors affecting the rampancy of brucellosis in various species of domestic animals. Outbreak of brucellosis could vary regarding environmental circumstances,

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geography, species, age and sex[11]. Despite the fact that Iran is an endemic area for brucellosis which is a serious public health issue in the country[12], few spatial studies of human brucellosis have been carried out up to now. Mollalo *et al*.[13] applied Moran's I index to find out possible clusters of human brucellosis incidences throughout Iran. By their research some hotspots in western, northwestern and northeastern parts of the country was found out. In addition, a meaningful positive correlation was observed between human brucellosis incidence and altitude; as a spatial parameter. Entezari *et al.*[14] examined the average annual climatic parameters including temperature, precipitation and humidity in Chaharmahal and Bakhtiari province of Iran from 2008 to 2011. Their outputs proved that there is a relevance between annual brucellosis incidence and annual average of the climatic factors dedicated to each county of their study area. Jia *at al.*[15] conducted spatial statistical analysis to study the epidemiology of human brucellosis in Inner Mongolia. They indicated that eastern and central parts of Inner Mongolia are the most appropriate endemic areas of the disease occurrence. Abdullayev *et al.*[16] tried to assess the spatio-temporal aspects of the epidemiology of brucellosis disease in Azerbaijan during 1995–2009. In their work, meaningful spatial clusters were determined in each of three, five-year periods with cumulative occurrence rates. Results also confirmed that the Ederer-Myer-Mantel (EMM) test can diagnose a surpassing number of statistically meaningful temporal clusters during 1995–1999.

In the study of Haghdoost *et al*.[17], some socio-economic parameters were taken into account and the possible association of these parameters with brucellosis incidence population in the rural sectors of Bardsir county of Kerman province in Iran was investigated. They found a positive correlation among the prevalence of brucellosis and the frequency of cattle; however, they could not find any significant association with some socio-economic indicators like accessibility to health facilities electricity. Their outcomes also proved that the majority of villages with higher risks were situated in the southern and northern parts of Bardsir. Ron *et al.*[18] carried out a surveillance with the aim of determining the Spatio-temporal distribution of incident human brucellosis cases in the continental Ecuadorian territory using municipality level between 1996 and 2008. In their paper, an analysis of the space–time distribution of human brucellosis cases was performed to identify areas with high risks of the disease. They also investigated the effects of cattle and small ruminant densities on the space–time distribution of human brucellosis cases. In addition, the effects of socio-economic variables and their interactions at the municipality level on the expected incidence of reported cases of human brucellosis were investigated using the zero-inflated Poisson regression and regression tree analyses.

There are also several papers based on statistical and spatial analyses to study the geographical prevalence of a disease. Smith *et al.*[19] using multilevel spatial models proved that the frequency of trichiasis and corneal opacity disease is highly affected by environmental parameters in Nigeria. In another research conducted by Teurlai *et al.*[20] principal component analysis and support vector machines were applied to show the impact of climatic conditions on the prevalence of dengue fever. They determined that although there is no any correlation with precipitation, the prevalence of the disease will be doubled with an increment of almost 3 °C in temperature by the end of 21st century.

Xu *et al*.[21] also tried to assess the associations between cholera infectious disease and environmental parameters with the help of geographical information systems and remote sensing. In their surveillance a meaningful relation was revealed between the disease incidence rate and temperature, rainfall, altitude and the distance to the shorelines. Kumar *et al.*[22] tried Pearson's correlation to distinguish influencing climatic factors on malaria disease in Chennai. Similarly, temperature and precipitation was concluded to be the environmental factors causing fluctuations in the rate of the disease incidence.

Understanding the spatio-temporal aspects of brucellosis can assist hygienic specialists and policy makers for taking viable measures to control and eradicate it. The crucial research arguments are: When the paramount temporal peak of prevalence occurs in Iran? Is there any statistically meaningful relation between temporal trends of disease, temporal swings of temperature, precipitation, wind speed and greenness in the country? Is there any momentous correspondence between incidence rate and vegetation cover of counties? By taking all these into the account, the major aims of this study would be applying GIS, temporal analyses and spatial statistics to assess the condition of this infectious disease to answer the questions above.

2. Materials and methods

2.1. Data collection and preparation

This study is performed in the whole country of Iran. According to the last submissions of political boundaries by Iranian Government in 2011, the country is divided into 31 provinces with total number of 386 counties. The political boundaries as well as their other statistical characteristics in the study period of time were obtainedby the Interior's Ministry (unpublished data). Approximately 95 per cent of the villages are covered by the country'swell founded healthcare network consisting of more than 16 000 rural sites. Health centers' employees and in charge executives are responsible for collecting the positive cases and their reliability[17].

In this research, a ward wise set of monthly human brucellosis passive data for a duration of 3 years from April 2009 to March 2012 were taken into account. This data consists of 39 359 cases officially announced by Tehran's Center for Disease Control and Prevention (CDC), which has been exhibited in Figure 1 as a cumulative occurrence GIS map. To promote the reliability of the data, Wright's test, 2-mercaptoethanol (2-ME) and Coombs & Wright's tests were applied on all the recorded cases as serological tests. Data consists of monthly reported cases and their occurrence location at the level of

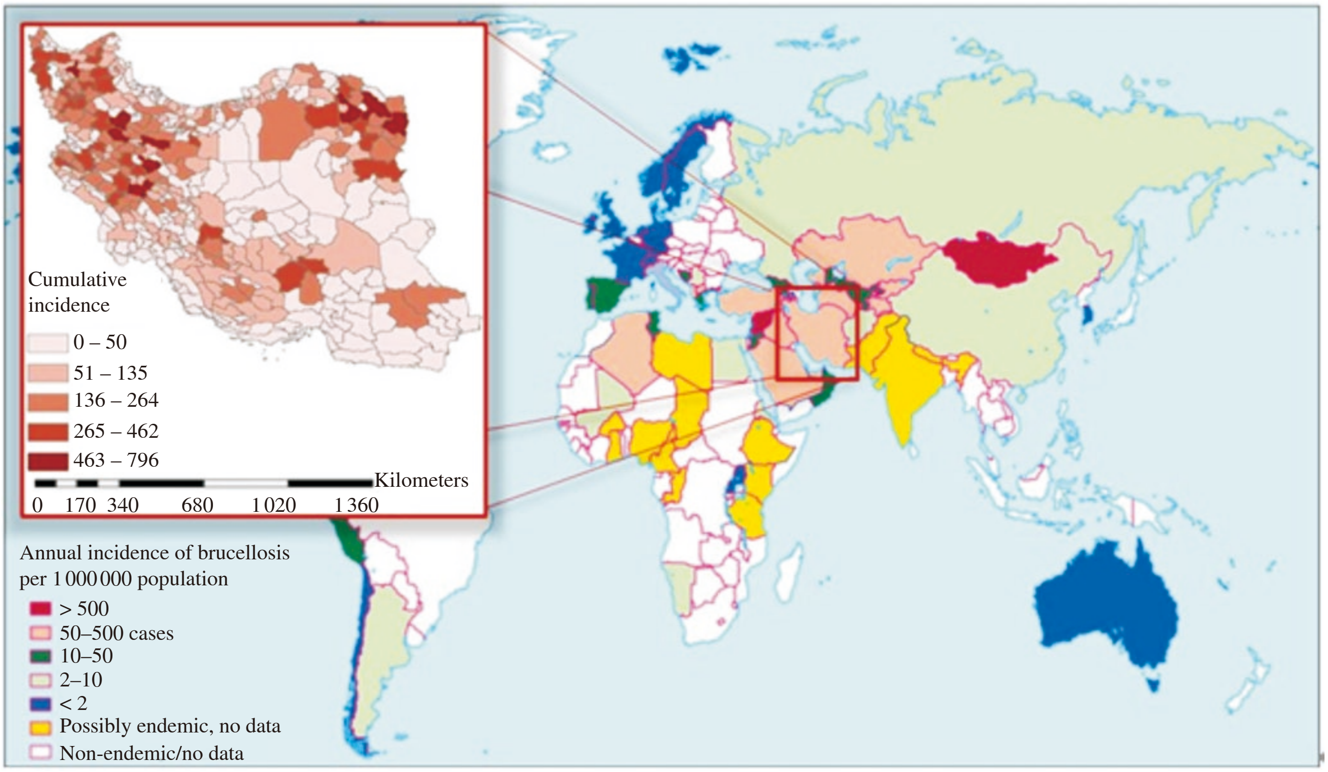

Figure 1. Worldwide occurrence of brucellosis and the critical status of Iran as an endemic area[10], cumulative incidence distribution during April 2009 to March 2012.

county. To address any possible uncertainty and duplication items, all the submitted patients were investigated meticulously. Subsequently, the data were attached to their corresponding geographic position at the level of county.

In addition, meteorological data including average precipitation, average temperature and average wind speed in monthly scale referring to the study period for each synoptic station throughout the country were received from Iran Meteorological Organization. Using Inverse Distance Weighting (IDW) interpolation technique an estimated value for each climatic parameter was provided for the whole country. Another environmental parameter, normalized difference vegetation index (NDVI) representing vegetation cover of the study area, was extracted from MODerate-resolution Imaging Spectroradiometer (MODIS) sensors on-board NASA's Terra and Aqua satellites imagery acquired in all 36 months between April 2009 and March 2012; provided from the United States Geological Survey (USGS). Furthermore, after performing some raster analyses, a unique mean NDVI value dedicated to each ward was produced and utilized in further inquiries.

Besides, monthly average values of four environmental factors including greenness, precipitation, wind speed and temperature were temporally aggregated, plotted and visually compared. Additionally, to spatially monitor the effect of specifically greenness on the incidence of human brucellosis, NDVI values for each months in each county were calculated and linked to their geographic location. These data were aggregated in each separate season, then, spatially mapped and visually compared with aggregated cumulative incidence rate in Figure 2.

2.2. Spatial and statistical analysis

Spatial and temporal perspectives as two main interests of scrutiny were taken into account in this study. Statistical analyses were used to investigate both spatial and temporal behavior of incidence trends and to survey environmental parameters and their impacts on the procedure. All statistical analyses were carried out using statistical software SPSS 18. The annual monthly average of human brucellosis cases were temporally accumulated for each year from April 2009 to March 2012 and plotted for a visual comparison. Subsequently, the rate of brucellosis incidence was calculated. The incidence rate of the disease is defined as the number of new cases of brucellosis which occur in a specific period of time in the corresponding population at risk for developing the disease. Thus, formula 1 was applied[23] and finally output. Incidence rate values were geo-referenced and linked to the corresponding polygons.

$$\text{Incidence rate per } 1\,000 = \frac{\text{No. of brucellosis disease occurrence in the population during a specific period of time}}{\text{No. of settlers exposed to the developing of the disease during that period of time}} \times 1\,000$$

Pearson's correlation coefficient, as the most frequently used parametric method was elected to investigate the possible association among human brucellosis incidence rates, climatic factors and geographical variables. Pearson's correlation coefficient computes the intensity and direction of the possible linear correlation between a pair of parameters. The coefficient values can fluctuate in the range of –1 to +1. A value of +1 implies that the relationship among the

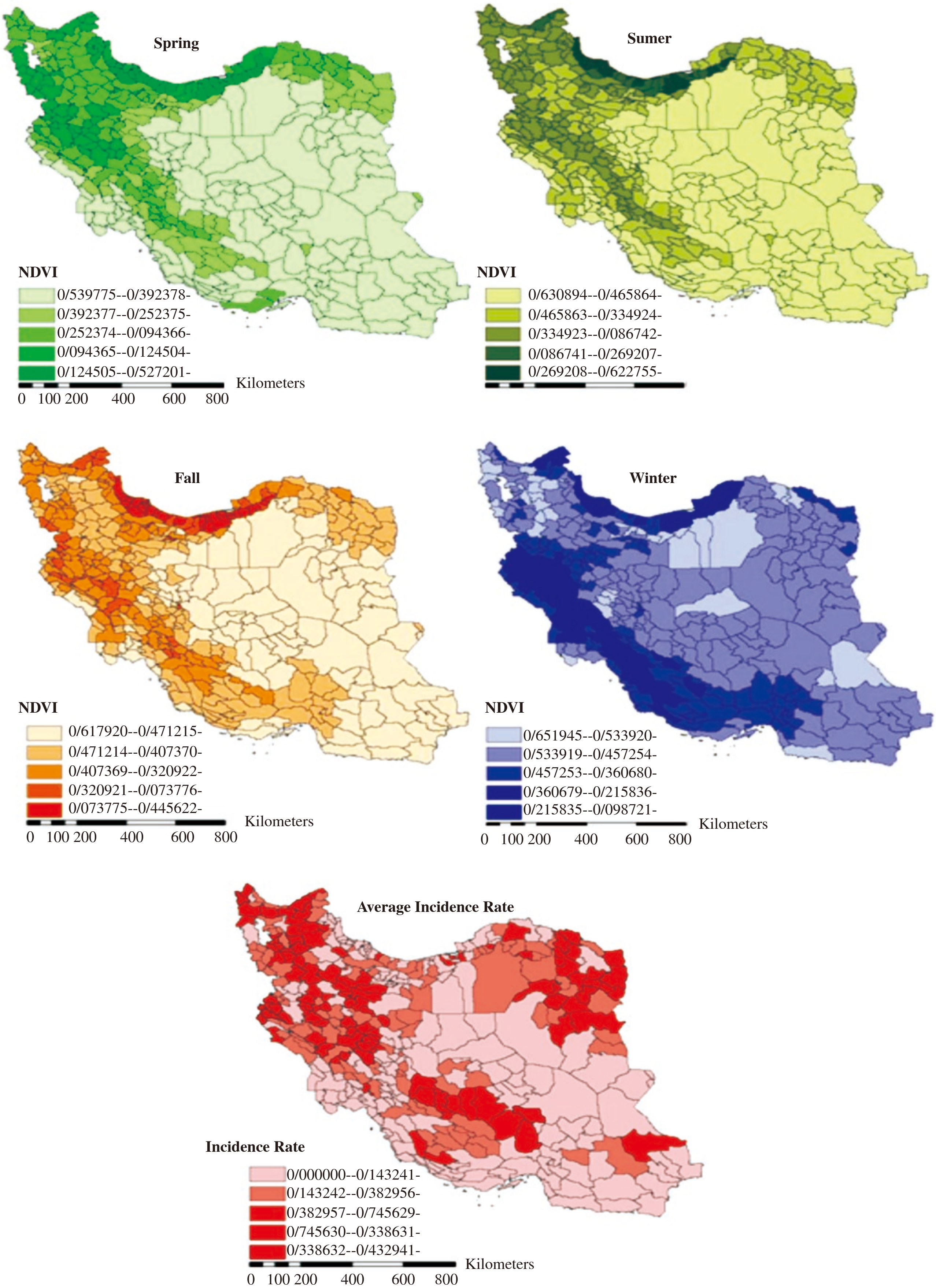

Figure 2. Seasonal aggregated vegetation cover of Iran, produced from MODIS NDVI image acquired and average incidence rate from April 2009 to March 2012.

variables is exactly linear and the strength of the linear relationship is maximum and they are correlated by an additive association, while a value of –1 represents a perfectly linear correlation between the parameters relating by a dwindling relation. In the cases that basically there is no linear correlation between the variables, the coefficient will take a value of nil[24]. Considering $\bar{p}$ and $\bar{q}$ as the means of variables P and Q respectively, and n as the number of total cases, the Pearson's correlation coefficient $\rho_{pearson}$ is defined as:

$$\rho_{pearson}(P, Q) = \frac{\sum_{i=1}^{n}(p_i - \bar{p})(q_i - \bar{q})}{\sqrt{\sum_{i=1}^{n}(p_i - \bar{p})^2 \sum_{i=1}^{n}(q_i - \bar{q})^2}}$$

Moreover, backward multiple linear regression was applied to find the best combination of four environmental factors to predict human brucellosis incidence. In multiple regression method, the final output would be written as follow. After creating the model, the parameter, R^2, measures the goodness of fit.

$$y = b_0 + b_1x_1 + b_2x_2 + ... + b_kx_k + \varepsilon$$

when y be modeled as a dependent variable; x_1 to x_k, are explanatory predicators, b_0, is the value of outcome when all considered independent variables are zero, b_1 to b_k, are regression coefficients and ε is the random error or disturbance term. As similar as the majority of statistical tests, multiple linear regression method also needs some assumptions about the contributing variables to be met. If the assumptions are not satisfied, results might be unreliable[25]. The following assumptions should be tested for a multiple linear regression procedure[24,26]:

1. The values of the residuals are normally distributed.
2. The relation between variables is linear.
3. The values of the residuals are independent.
4. The values of the residuals are constant (homoscedasticity).

To survey the quadripartite assumptions several tests were performed. Since normality is a required feature of data points for generally parametric methods such as Pearson's correlation and linear regression which have been used in this study, all data sets were normalized using rank-based inverse normal transformations (INTs). Table 1 shows the outputs of Shapiro-Wilk and Kolmogorov-Smirnov tests of normality for all data sets ($P > 0.05$). As it is apparent from Figure 3, there are strong linear relationship among considered independent variable (brucellosis) and other dependent ones, therefore, the assumption of linearity was met. However, strong associations were found between some of predicators, which may violate the assumption of independence. Since a backward multiple regression excludes collinear predictors, then, this violation was also addressed. Finally, Figure 4 demonstrates that the last assumption, homoscedasticity, was also met.

Table 1

Normality tests of variables.

Variables	Kolmogorov-Smirnov		Shapiro-Wilk	
	Statistic	Sig.	Statistic	Sig.
Brucellosis	0.051	0.200	0.990	0.992
Precipitation	0.039	0.200	0.990	0.991
Temperature	0.046	0.200	0.992	0.997
Wind	0.038	0.200	0.994	1.000
NDVI	0.038	0.200	0.994	0.999

3. Results

The monthly average trends of four meteorological and greenness factors, the monthly average of human brucellosis incidence rate for all 386 counties of the country, and their associations have been presented in Table 2 and visually depicted in Figure 5. According to Table 2, Pearson's correlation analysis revealed that there are positive correlations between disease monthly average incidence and the aggregated monthly average greenness, temperature and wind speed at the 0.01 level of significance. Besides, a strong negative association was observed between the disease monthly average incidence and the monthly average precipitation at the 0.01 significance level.

Table 2

Pearson's correlation coefficients between monthly average human brucellosis occurrence and monthly average environmental factors for April 2009 to March 2012.

		Brucellosis	Precipitation	Temperature	Wind speed	NDVI
Brucellosis	Pearson correlation	1	–0.569**	0.696**	0.706**	0.693**
	Sig. (2-tailed)		0.000	0.000	0.000	0.000
	N	35	34	34	34	34
Precipitation	Pearson correlation	–0.569**	1	–0.794**	–0.345*	–0.416*
	Sig. (2-tailed)	0.000		0.000	0.046	0.014
	N	34	35	34	34	34
Temperature	Pearson Correlation	0.696**	–0.794**	1	0.546**	0.635**
	Sig. (2-tailed)	0.000	0.000		0.001	0.000
	N	34	34	35	34	34
Wind Speed	Pearson Correlation	0.706**	–0.345*	0.546**	1	0.653**
	Sig. (2-tailed)	0.000	0.046	0.001		0.000
	N	34	34	34	35	34
NDVI	Pearson Correlation	0.693**	–0.416*	0.635**	0.653**	1
	Sig. (2-tailed)	0.000	0.014	0.000	0.000	
	N	34	34	34	34	35

*: Correlation is significant at the 0.05 level (2-tailed); **: Correlation is significant at the 0.01 level (2-tailed).

In the case of spatial survey of vegetation cover which is shown in Table 3, a drastic association (0.01 level of significance) observed between seasonal cumulative average incidence rates and NDVI values in spring. This relationship gets somehow weaker in summer with the significance level of 0.05. Results also showed that there is no considerable correlation with fall season. Interestingly, the correlation meaningfully turns to negative in winter (0.01 significance level).

Table 3

Pearson's correlation coefficients between cumulative human brucellosis incidence rates and aggregated NDVI values for each season.

		Spring NDVI	Summer NDVI	Fall NDVI	Winter NDVI	Cumulative incidence rate
Spring NDVI	Pearson Correlation	1	0.942**	0.896**	0.483**	0.163**
	Sig. (2-tailed)		0.000	0.000	0.000	0.001
	N	385	384	384	384	384
Summer NDVI	Pearson Correlation	0.942**	1	0.926**	0.422**	0.128*
	Sig. (2-tailed)	0.000		0.000	0.000	0.012
	N	384	385	384	384	384
Fall NDVI	Pearson Correlation	0.896**	0.926**	1	0.674**	0.047
	Sig. (2-tailed)	0.000	0.000		0.000	0.361
	N	384	384	385	384	384
Winter NDVI	Pearson Correlation	0.483**	0.422**	0.674**	1	-0.146**
	Sig. (2-tailed)	0.000	0.000	0.000		0.004
	N	384	384	384	385	384
Cumulative incidence rate	Pearson Correlation	0.163**	0.128*	0.047	–0.146**	1
	Sig. (2-tailed)	0.001	0.012	0.361	0.004	
	N	384	384	384	384	385

*: Correlation is significant at the 0.05 level (2-tailed); **: Correlation is significant at the 0.01 level (2-tailed).

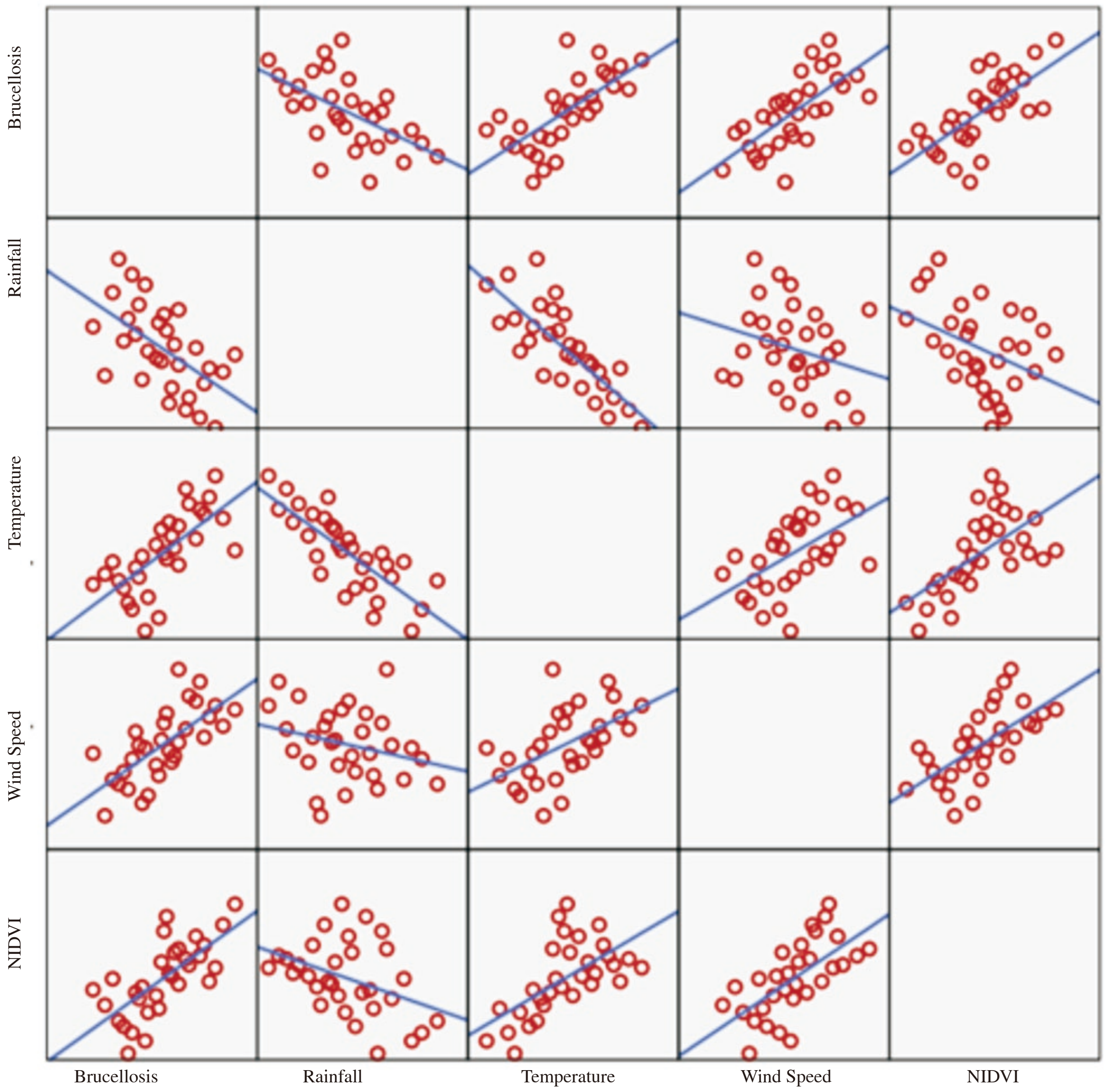

Figure 3. The co-linearity scatter plots of the variables.

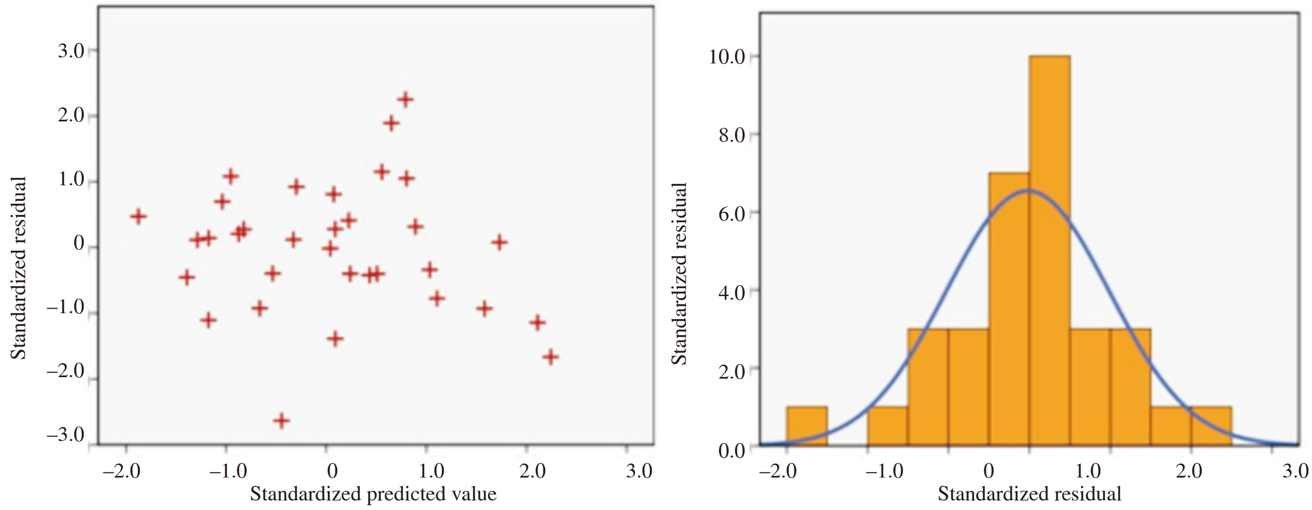

Figure 4. The scatter plot of the residuals and their normal chart.

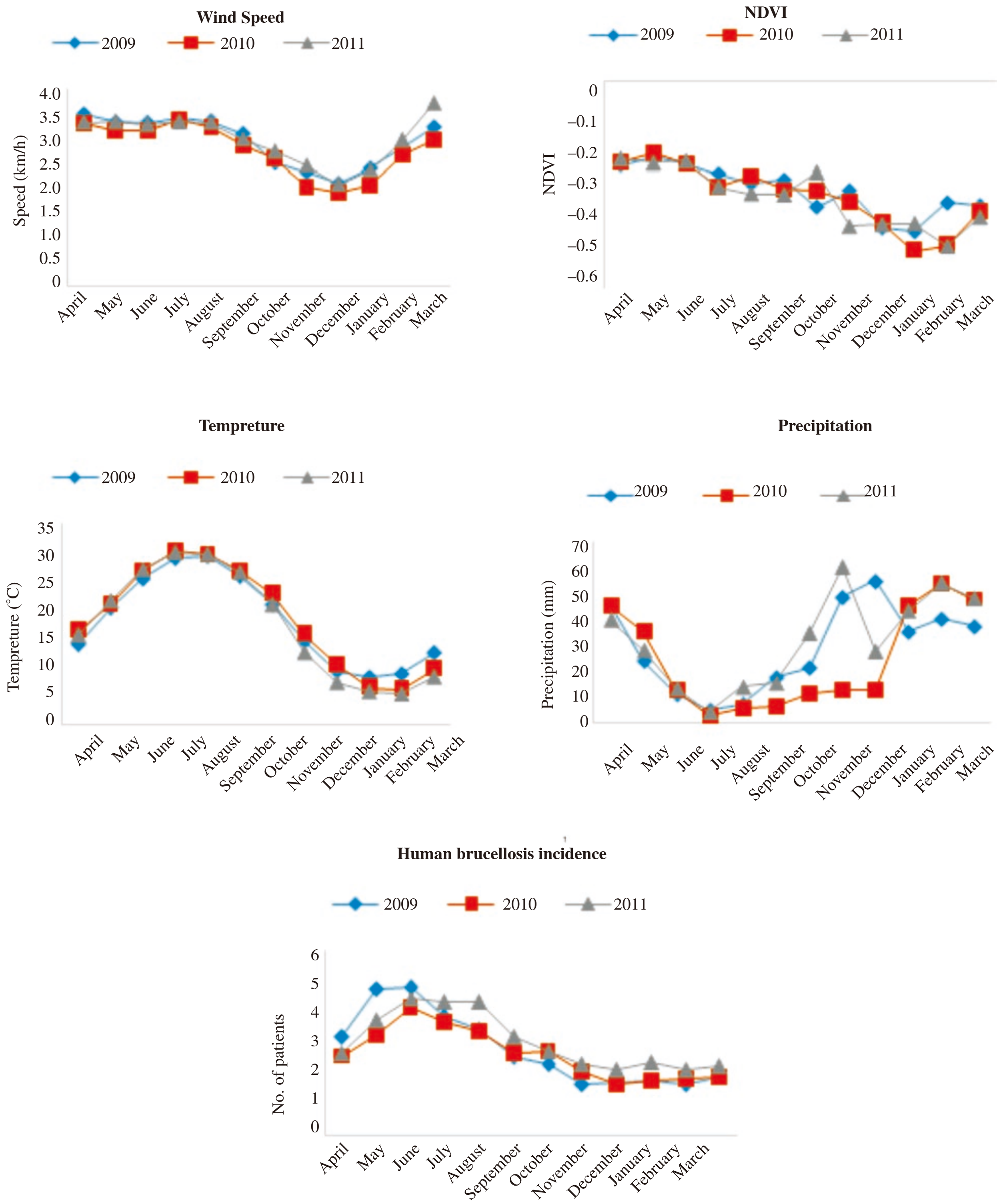

Figure 5. The trends of monthly average human brucellosis incidence, NDVI, wind speed, temperature and precipitation from April 2009 to March 2012.

Table 4

The summary of backward multiple linear regression for four environmental factors as independent variables and the human brucellosis incidence rate as a dependent variable.

Model	R	R^2	Adjusted R^2	Std. error of the estimate	Change Statistics					Durbin-Watson
					R^2 change	F change	df1	df2	Sig. F change	
1	0.983[a]	0.967	0.962	0.57217157	0.967	198.678	4	27	0.000	
2	0.983[b]	0.966	0.962	0.57346844	–0.001	1.127	1	27	0.298	
3	0.982[c]	0.965	0.962	0.57255007	–0.001	0.907	1	28	0.349	1.664

[a]: Predictors – NDVI, temperature, precipitation, wind speed; [b]: Predictors – Temperature, precipitation, wind speed; [c]: Predictors – Precipitation, wind speed (chosen model).

Table 5

Coefficient matrix of final multiple regression model for human brucellosis disease as a dependent variable.

Model	Unstandardized coefficients		Standardized coefficients	t	Sig.	Correlations			Co-linearity statistics	
	B	Std. Error	Beta			Zero-order	Partial	Part	Tolerance	VIF
Precipitation	–0.024	0.006	–0.273	–4.078	0.000	0.756	–0.604	–0.142	0.271	3.688
Wind Speed	1.215	0.068	1.205	17.977	0.000	0.972	0.958	0.628	0.271	3.688

After performing backward multiple linear regression, the third model including wind speed and precipitation with $R^2 = 0.965$ and the lowest variance inflation factor (VIF = 3.688) was opted as the best fitted model among all proposed models (Table 4). It is concluded that 0.965 changes of monthly human brucellosis incidence was contributed to the monthly average rainfall, and wind speed. Regarding the coefficients obtained from the backward multiple linear regression, which are shown in Table 5, the best model among others, with the highest R, R^2, and the lowest P-value ($P < 0.01$) was the regression model with the following equation:

$$Z = 1.215 \times WS - 0.024 \times PRE$$

where WS stands for wind speed and PRE represents precipitation.

4. Discussion

The outputs of this article are considered as both extension and support for findings of the previous study on the human brucellosis disease in Iran[13] and the essay of zoonotic cutaneous leishmaniasis (ZCL) disease[27]. According to the line chart, presented in Figure 5, the rate of incidence starts an upswing trend steeply from February of each year. This growth continues almost up to the peak month June, then, a steady downward trend begins and finishes to the end of the year, where the incidence rate remains stable for the rest of the year. Interestingly the peak of the epidemic is from February to June and is nearly associated with the period of sheep's delivery and abortion[28].

Considering Pearson's correlation coefficients, all the surveyed parameters in this work showed a strong association with human brucellosis incidences throughout the country in the studied period of time. Among all factors, temperature, wind speed and greenness showed strong positive correlations, however, precipitation had a strong negative association with human brucellosis disease. These results are consistent with those of Entezari *et al.*[14] who found the warm months with the lowest rainfall and the highest temperature are more susceptible to disease outbreaks. Although they had studied annual average of some climatic features spatially, the results of temporal surveys of this paper were almost supplementary. They are also consistent with the previous findings of Mollalo *et al*.[29] and Mollalo and Khodabandehloo[30] who observed a significant association between vegetation cover and cutaneous leishmaniasis (CL) incidence in Golestan Province of Iran, however, the direction of the correlation varies. And also in other researches performed by Mollalo *et al*.[31] and Sofizadeh *et al.*[32] similar results were derived. They carried out a cross sectional study on zoonotic cutaneous leishmaniasis (ZCL) disease and found out that the majority of the ZCL cases were occurred in arid and semi-arid climates.

Interestingly, NDVI values are positively correlated with the average cumulative incidence rate of the brucellosis in spring and slightly in summer, however, there is a meaningful descending trend. The correlation in fall was negligible while, there is a remarkable negative correlation in winter (Table 3). Based on these findings, the fact that human brucellosis disease is more likely to occur in zones having green spring and summer and dry winter might be conclusive. And also temporal circumstances with high temperature, wind speed and overall greenness and low precipitation are more suitable for brucellosis occurrence.

By taking the results of backward multiple linear regression the following conclusion is derivable; 1.215 is an estimate of the expected increase in brucellosis cases corresponding to a unit increase in wind speed when precipitation is held constant. Similarly, 0.024 is an approximation of the anticipated decrease in the disease cases corresponding to a unit growth in rainfall when wind speed is remained unchanged.

A critical restriction of this research might be the deficiency of data. Absolutely there are so many factors contributing in the occurrence of a disease such as some socio-economic factors and other climatic parameters which are passed up in this surveillance. Another limitation would be related to the current superintendence system of the country that may not be efficient enough in some aspects such as missing a considerable amount of patients or unreliable official reports. Thus, there might be a possibility that some occurrence items be miscalculated. Forasmuch as the case submission system has been unchanged in the study period, the distribution of these errors are almost even throughout the country and can be considered as the elimination errors.

Since the registration system of human brucellosis is uniform throughout Iran, these errors are evenly distributed and may happen everywhere. Thus, the errors can be regarded as the omission errors. The distribution of human brucellosis disease seems to be spatially clustered. In addition, the prevalence of the disease is considerably affected by climatic conditions and environmental factors. Locations with higher greenness, temperature, and wind speed are more susceptible to face surpassing rates of the disease. Contrast results of rainfall is inclusive. Counties with higher greenness in spring and summer are more likely to be an appropriate host for more incidences. These finding can provide essential guidelines for public health policy makers and widen their horizon to monitor and estimate the disease occurrence trend based on the environmental identities for future control plans.

Conflict of interest statement

We declare that we have no conflict of interest.

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References

[1] Zhang J, Sun GQ, Sun XD, Hou Q, Li MT, Huang BX, et al. Prediction and control of brucellosis transmission of dairy cattle in Zhejiang Province, China. *Plos One* 2014; **9**(11): e108592.

[2] Radostits OM, Blood DC, Henderson JA. *Veterinary medicine*. London: Balliere Tindall; 2000.

[3] Cripps PJ. Veterinary education, zoonoses and public health: a personal perspective. *Acta Trop* 2000; **76**: 77-80.

[4] Gwida M, Al Dahouk S, Melzer F, Rösler U, Neubauer H, Tomaso H. Brucellosis–regionally emerging zoonotic disease? *Croat Med J* 2010; **51**: 289-95.

[5] Zowghi E, Ebadi A, Yarahmadi M. Isolation and identification of *Brucella* organisms in Iran. *Iran J Clin Infect Dis* 2009; **3**: 185-8.

[6] Lopes LB, Nicolino R, Haddad JPA. Brucellosis-risk factors and prevalence: a review. *Open Vet Sci J* 2010; **4**: 72-84.

[7] Plumb GE, Olsen SC, Buttke D. Brucellosis: 'One Health' challenges and opportunities. *Revue Sci Tech* 2013; **32**(1): 271-8.

[8] Kafil HS, Hosseini SB, Sohrabi M, Asgharzadeh M. Brucellosis: presence of zoonosis infection 3500 years ago in North of Iran. *Asian Pac J Trop Dis* 2014; **4**: S684-6.

[9] World Organisation for Animal Health. Handistatus II: zoonoses (human cases): global cases of brucellosis in 2003. Paris: World Organisation for Animal Health; 2003. [Online] Available from: http://www.oie.int/hs2/gi_zoon_mald.asp?c_cont=6&c_mald=172&annee=2003 [Accessed on 13th December, 2005]

[10] Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos EV. The new global map of human brucellosis. *Lancet Infect Dis* 2006; **6**: 91-9.

[11] Gul ST, Khan A. Epidemiology and epizootology of brucellosis: a review. *Pak Vet J* 2007; **27**: 145.

[12] Esmaeili H. Brucellosis in Islamic Republic of Iran. *J Med Bacteriol* 2015; **3**: 47-57.

[13] Mollalo A, Alimohammadi A, Khoshabi M. Spatial and spatio-temporal analysis of human brucellosis in Iran. *Trans Royal Soc Trop Med Hyg* 2014; **108**(11): 721-8.

[14] Entezari M, Moradpour S, Amiri M. Spatial distribution and the impact of geographical factors on brucellosis in Chaharmahal and Bakhtiari Province, Iran. *Int J Epidemiol Res* 2016; **3**: 98-105.

[15] Jia P, Joyner A. Human brucellosis occurrences in Inner Mongolia, China: a spatio-temporal distribution and ecological niche modeling approach. *BMC Infect Dis* 2015; **15**: 36.

[16] Abdullayev R, Kracalik I, Ismayilova R, Ustun N, Talibzade A, Blackburn JK. Analyzing the spatial and temporal distribution of human brucellosis in Azerbaijan (1995-2009) using spatial and spatio-temporal statistics. *BMC Infect Dis* 2012; **12**: 185.

[17] Haghdoost AA, Kawaguchi L, Mirzazadeh A, Rashidi H, Sarafinejad A, Baniasadi A, et al. Using GIS in explaining spatial distribution of brucellosis in an endemic district in Iran. *Iran J Public Health* 2007; **36**: 27-34.

[18] Ron L, Benitez W, Speybroeck N, Ron J, Saegerman C, Berkvens D, et al. Spatio-temporal clusters of incident human brucellosis cases in Ecuador. *Spatial Spatio-temporal Epidemiol* 2013; **5**: 1-10.

[19] Smith JL, Sivasubramaniam S, Rabiu MM, Kyari F, Solomon AW, Gilbert C, et al. Multilevel analysis of trachomatous trichiasis and corneal opacity in Nigeria: the role of environmental and climatic risk factors on the distribution of disease. *PLoS Negl Trop Dis* 2015; **9**(7): e0003826.

[20] Teurlai M, Menkès CE, Cavarero V, Degallier N, Descloux E, Grangeon JP, et al. Socio-economic and climate factors associated with Dengue fever spatial heterogeneity: A worked example in New Caledonia. *PLoS Negl Trop Dis* 2015; **9**(12): e0004211.

[21] Xu M, Cao CX, Wang DC, Kan B, Xu YF, Ni XL, et al. Environmental factor analysis of cholera in China using remote sensing and geographical information systems. *Epidemiol Infect* 2016; **144**(5): 940-51.

[22] Kumar DS, Andimuthu R, Rajan R, Venkatesan MS. Spatial trend, environmental and socioeconomic factors associated with malaria prevalence in Chennai. *Malar J* 2014; **13**: 14.

[23] Gordis L. *Epidemiology*. Philidelphia: Saunders Elsevier; 2014.

[24] Cohen J, Cohen P, West SG, Aiken LS. *Applied multiple regression/correlation analysis for the behavioral sciences*. Abingdon-on-Thames: Routledge; 2013.

[25] Harrell F. *Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis*. New York: Springer; 2015.

[26] Field A. *Discovering statistics using IBM SPSS statistics*. Thousand Oaks: Sage; 2013.

[27] Shirzadi MR, Mollalo A, Yaghoobi-Ershadi MR. Dynamic relations between incidence of zoonotic cutaneous leishmaniasis and climatic factors in Golestan Province, Iran. *J Arthropod Borne Dis* 2015; **9**: 148-60.

[28] Shang DQ, Xiao DL, Yin JM. Epidemiology and control of brucellosis in China. *Vet Microbiol* 2002; **90**: 165-82.

[29] Mollalo A, Alimohammadi A, Shahrisvand M, Shirzadi MR, Malek MR. Spatial and statistical analyses of the relations between vegetation cover and incidence of cutaneous leishmaniasis in an endemic province, northeast of Iran. *Asian Pac J Trop Dis* 2014; **4**: 176-80.

[30] Mollalo A, Khodabandehloo E. Zoonotic cutaneous leishmaniasis in northeastern Iran: a GIS-based spatio-temporal multi-criteria decision-making approach. *Epidemiol Infect* 2016; **144**: 2217-29.

[31] Mollalo A, Alimohammadi A, Shirzadi MR, Malek MR. Geographic information system-based analysis of the spatial and spatio-temporal distribution of zoonotic cutaneous leishmaniasis in Golestan Province, north-east of Iran. *Zoonoses Public Health* 2015; **62**(1): 18-28.

[32] Sofizadeh A, Rassi Y, Vatandoost H, Hanafi-Bojd AA, Mollalo A, Rafizadeh S, et al. Predicting the distribution of *Phlebotomus papatasi* (Diptera: Psychodidae), the primary vector of zoonotic cutaneous leishmaniasis in Golestan Province of Iran using ecological niche modeling: comparison of MaxEnt and GARP models. *J Med Entomol* 2017; **54**: 312-20.