An investigation of the effects of environmental and ecologic factors on cutaneous leishmaniasis in the old world: a systematic review study

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Abstract

Objectives: Leishmaniasis is a neglected and widespread parasitic disease that can lead to serious health problems. The current review study aimed to synthesize the relationship between ecologic and environmental factors (e.g., weather conditions, climatology, temperature and topology) and the incidence of cutaneous leishmaniasis (CL) in the Old World.

Content: A systematic review was conducted based on English, and Persian articles published from 2015 to 2020 in PubMed/Medline, Science Direct, Web of Science and Google Scholar. Keywords used to search articles were "leishmaniasis, environmental factors, weather condition, soil, temperature, land cover, ecologic* and topogr*. All articles were selected and assessed for eligibility according to the titles or abstracts. The quality screening process of articles was carried out by two independent authors. The selected articles were checked according to the inclusion and exclusion criteria.

Summary and outlook: A total of 827 relevant records in 2015–2020 were searched and after evaluating the articles, 23 articles met the eligibility criteria; finally, 14 full-text articles were included in the systematic review. Two different categories of ecologic/environmental factors (weather conditions, temperature, rainfall/precipitation and humidity) and land characteristics (land cover, slope, elevation and altitude, earthquake and cattle sheds) were the most important factors associated with CL incidence.

Conclusions: Temperature and rainfall play an important role in the seasonal cycle of CL as many CL cases occurred in arid and semiarid areas in the Old World. Moreover, given the findings of this study regarding the effect of weather conditions on CL, it can be concluded that designing an early warning system is necessary to predict the incidence of CL based on different weather conditions.

Keywords: cutaneous leishmaniasis; ecologic; environmental factors; review; weather condition.

Introduction

Leishmaniasis is a serious public health problem in the world that is considered a re-emerging international vector-borne human disease [1, 2]. Phlebotomine sandflies are the vectors of its parasite named *Leishmania* [1]. Leishmaniasis has two important types: cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL). CL is one of the important, but mostly neglected, endemic tropical diseases in Iran [2, 3].
According to the report published by the World Health Organization (WHO) in 2019, the annual incidence of leishmaniasis has been estimated to range from 700,000 to 1.2 million in the world [4, 5]. It is estimated that the incidence of leishmaniasis is more than 12 million cases worldwide, and 1.5–2 million new cases are added to this rate annually, 75% of which are of cutaneous forms [6]. CL is hard to treat because no vaccine is yet available [3].

The majority of CL wounds have been observed on the hands (62.75%), head/neck (24.8%) and body (2.7%) [7]. A more prevalent symptom of CL is a single and self-healing cutaneous lesion that might proceed to a persistent, metastatic disease with granulomatous nodules affecting multiple secondary sites on the skin and resulting in delicate facial mucosa, which can sometimes diffuse throughout the cutaneous system. The basis for such diverse pathologies is multifactorial, ranging from parasite phylogeny to host immunocompetence and various environmental factors [8].

About 102 countries have reported leishmaniasis, and more than 90% of the total new cases of leishmaniasis have occurred in eight countries [7, 9]. Based on the WHO report in 2019, over 95% of new CL cases in 2017 occurred in six countries including Afghanistan, Algeria, Brazil, Colombia, Iraq, the Syrian Arab Republic and Islamic Republic of Iran [4]. CL in the Old World was caused by *Leishmania tropica* (more common in the Mediterranean Basin, the Middle East, Pakistan and India) and *Leishmania infantum* (sporadically in the Middle East, South Russia and rural regions of Africa). Moreover, CL is heavily dependent on some demographic and socioeconomic factors such as poverty [3], male gender, rurality and childhood age [7, 10].

Leishmaniasis is an important parasitic disease prevalent around the world with serious health effects related to weather conditions [11]. Spatial analyses in different studies have shown that environmental factors, such as weather conditions, are the most important factors playing a role in CL incidence [1, 11, 12]. According to a review study, CL incidence varies in different provinces of Iran from 1.8 to 37.9%. The geographic distribution of CL disease shows that CL cases mostly occur in the east, center and southern regions of Iran, and 62.6% of CL cases live in rural areas [7]. Thus, to prevent and control CL, effective and appropriate strategies need to be developed and the spatial pattern and detecting hotspots of CL should be carefully studied [1, 11, 12]. The epidemiology and morbidity of CL are related to weather conditions and other environmental factors that are related to the composition, distribution and behavior of sand flies as the main vector species [13]. CL vectors are mainly distributed in forests, soil lands, disturbed environments and dry farms [14–16]. Inconclusive findings have been observed in the results of numerous studies investigating the role of weather conditions on CL in different countries, especially in terms of relative humidity [17, 18], rainfall [15, 19] and lag of time in temperature and humidity [15, 17]. Hence, this study aimed to assess the degree to which CL incidence was dependent on weather conditions and other environmental factors in the Old World.

### Materials and methods

A systematic review was conducted based on English and Persian articles published from 2015 to 2020 (23 March) in four databases including PubMed/Medline, Science Direct, Web of Science and Google Scholar. All the related articles were selected and assessed to find the eligible articles whose titles or abstracts addressed leishmaniasis or environmental factors related to leishmaniasis. The references of related articles were also searched and used in the review. The quality screening process of articles was carried out by two independent authors. The selected articles were checked in terms of inclusion and exclusion criteria.

**Inclusion criteria:** Epidemiological (ecological and cross-sectional) studies assessing the associations between leishmaniasis and environmental factors (e.g., weather conditions, elevation, humidity, temperature, rainfall, soil cover, land cover, ecological factors and land topography) were included. All the articles that were published in six years (August 2015 to March 2020) in English and Persian languages about countries in the Old World, especially Eastern Mediterranean Region (EMRO) including Afghanistan, Turkey, Islamic Republic of Iran, Iraq, Syrian Arab Republic and Algeria were included in the study.

**Exclusion criteria:** The following studies were excluded from the review: therapeutic studies that evaluated the effect of heat, cold or other environmental factors in the treatment of leishmaniasis, the randomized clinical trials, studies that assessed the incidence of the disease in animals such as dogs, all studies that were published in the proceedings of symposiums or conferences, unpublished literature, studies with confusing results or incomprehensible analyses and studies exhibiting bias or inconsistencies in their findings.

### Search strategy

After framing review questions regarding the effects of environmental factors on CL, relevant studies were searched and detected. Four databases, including PubMed/Medline, Google Scholar, Web of Science and Science Direct, were searched to find eligible articles. The keywords and search strategy included leishmaniasis, environmental factors, climate, weather condition, soil, temperature, land cover, ecologic* and topogr*.

### Data extraction

After the full consideration of all databases based on the keywords, the proper records were entered into EndNote X8 (Thomson Reuters, New
transmission of CL [11]. In another study, Nikonahad et al. [28] revealed a significant association between environmental/meteorological variables and CL incidence by the SARIMA models. Their results indicated that more robust preventive programs are needed in earthquake-prone areas and inceptisol soil type than needed in other areas [28]. The temperature at a lag of five months and relative humidity are the effective environmental factors in the occurrence of CL cases, and the effect of temperature seems to enhance in higher humidities [17]. Besides, according to the Ordinary Least Square (OLS) model in Ramezankhani et al.’s study, temperature and humidity were the most important environmental factors of CL incidence. Moreover, it was observed that whereas temperature had direct effects on CL incidence, humidity exerted inverse effects [18]. Similar results were also reported by Ghatee et al. [21] and Chavy et al. [26]. In another study, Sharaft et al. reported that the amount of evaporation, the number of sunny days, the rate of wind velocity and temperature had direct effects on the incidence of CL [29].

Quality assessment

The assessment of the quality of studies was carried out based on the STROBE checklist of observational studies. Each article was assessed independently by two authors, and then the data were extracted independently. Another author acted as an arbiter to resolve any disagreements. Then, the important bibliographical information and the main results of each article were extracted and summarized. The results and interpretation of the findings are presented in the results section and Table 1.

Results

The literature search and selection process are depicted in Figure 1. A total of 827 relevant articles and their references were initially searched in the four databases. After removing duplicates in the Endnote software, 362 articles remained for the screening process based on the titles and abstracts. During the screening process, 294 articles were removed by checking the titles and abstracts, and 68 articles were checked to be full-text articles. After evaluation, 45 full-text articles were removed, and 23 full-text articles met the eligibility criteria for the systematic review. Finally, after removing nine articles, 14 full-text articles were included in the systematic review (shown in Table 1) [1, 6, 9, 11, 12, 15–30]. Based on the findings, the effects of environmental factors on the incidence of CL in the Old World are discussed below.

Weather conditions

Weather patterns can provide a favorable condition for the propagation and transmission of leishmaniasis in endemic areas [11]. CL incidence was higher in areas with daily rainfalls, maximum/minimum temperature and humidity, and these environmental factors occurred mostly in hyperendemic areas of CL compared to the low-endemic ones. The substantial climatic variability in 2010–2014 in Khuzestan Province, Iran, was mentioned as the main reason for the change in the epidemiology and transmission of CL [11]. In another study, Nikonahad et al.
Table 1: The summary of studies included in this review based on the extracted data.

| Row | Authors, year | Objective | Place | Sample size | Statistical analysis | Variables | Main results | Positive significant variables on CL incidence | Negative/non-significant variables on CL incidence |
|-----|---------------|-----------|-------|-------------|----------------------|-----------|--------------|-----------------------------------------------|-----------------------------------------------|
| 1   | Ghatee et al. [21], 2018 | The effect of environmental factors and closeness, proximity to cattle and sheep/goat sheds on the occurrence of CL | Kohgiluye and Boyerahmad (K–B) province, Iran | 275 CL patients during a 5-year period | Univariate and two multivariate logistic regression models, Geographical information systems (GIS) | Minimum, maximum, and mean annual of temperature, mean annual rainfall, slope, elevation, land covers and closeness, proximity to cattle and sheep/goat sheds | Land cover, ground slope, elevation and closeness, proximity to cattle sheds were the most effective factors of CL incidence. The incidence of CL can increase in urban areas, dry farms, thin rangelands and land covers, but slopes and elevation can decrease the occurrence of the disease | –: Land cover, –: Ground slope | –: Closeness, proximity to cattle sheds |
| 2   | Sharafi M et al., 2019 [29] | To assess the relationship between the geographical factors and CL incidence using spatial analysis | Fasa, Iran | 2009 to 2014 | Ordinary least square (OLS) and global Moran’s index (GMI) | Means of temperature, humidity, rainfall, sunny days, rainy days, and evaporation | Maximum temperature, mean of temperature, mean of evaporation, sunny days and wind velocity were the factors affecting the high incidence of CL | –: Maximum temperature, –: Mean of evaporation, –: Wind velocity | –: Mean of temperature, –: Number of sunny days |
| 3   | Artun O, 2019 [23] | To develop a model based on ecological niche modeling (ENM) to predict the distribution of CL in endemic areas of Turkey | Adana, Turkey | 1,831 native CL cases at 2017 | Jackknife analysis and area under the curve (AUC) | Environmental and ecological determinants | Annual mean temperature and temperature seasonality digital elevation model were associated with environmental factors of the presence of human cases of Leishmania infantum | –: Annual mean temperature | –: Elevation |
| 4   | Artun O, 2019 [24] | To determine the distribution of disease in two endemic foci and comparison of variables in terms of CL epidemiology | Eastern Mediterranean region | 2548 CL patients from 2008 to 2015 | Jackknife analysis and area under the curve (AUC) | Bio-climatic and environmental variables | The maximum temperature of the warmest month, mean temperature of the driest quarter and mean temperature of the warmest quarter were the more effective factors of CL case distribution in | –: Annual mean temperature | –: Elevation |

Mohammadbloo et al.: Review of environmental factors of leishmaniasis
| Row | Authors, year | Objective | Place | Sample size | Statistical analysis | Variables | Main results | Positive significant variables on CL incidence | Negative/non-significant variables on CL incidence |
|-----|---------------|-----------|-------|-------------|----------------------|-----------|--------------|---------------------------------------------|------------------------------------------------|
| 5   | Adegboye MA et al., 2019 [30] | To assess the time-varying meteorological variables of leishmaniasis | Afghanistan | 2003–2009 | Distributed lag non-linear model, Poisson regression | Population, seasonality, long-term trend with meteorological variables - temperature (°C) and rainfall | Leishmaniasis during the cold temperature was the highest at moderate cold temperature. The overall risk of leishmaniasis-temperature was estimated to be 7.6% and mostly due to cold temperature | Maximum temperature of the warmest month, |
|     |               |           |       |             |                      |           |              | Mean temperature of the driest quarter mean temperature of the warmest quarter |
| 6   | Ramezankhani et al.[1] 2018 | To identify the climate and environmental factors associated with CL incidence | Isfahan province, Iran | From 2007 to 2015 | Generalized linear models (GLMs), negative binomial regression | Seven climate and environmental factors | Seven climate and environmental factors explained 40% of the deviance of CL incidence | Maximum temperature, |
|     |               |           |       |             |                      |           |              | Relative humidity, |
| 7   | Ramezankhani et al. 2017 [12] | To identify the hotspot areas for CL in isfahan and assess the relationships between the climatic and | Isfahan province, Iran | From 2011 to 2015 | Spatial analysis, global Moran’s index, Vegetation coverage, altitude and climatic data | Relative humidity of 27–30%, mean temperature of 15–19 degrees C, mean precipitation of 5–20 mm, maximum wind | Relative humidity of 27–30%, mean temperature of 15–19 degrees C, mean precipitation of 5–20 mm, maximum wind | |
|     |               |           |       |             |                      |           |              | Vegetation cover |

mersin. The mean diurnal range and mean temperature of the coldest quarter were significantly related to CL incidence in diyarbakir.
Table 1: (continued)

| Row | Authors, year | Objective | Place | Sample size | Statistical analysis | Variables | Main results | Positive significant variables on CL incidence | Negative/non-significant variables on CL incidence |
|-----|---------------|-----------|-------|-------------|----------------------|-----------|--------------|-----------------------------------------------|-----------------------------------------------|
| 8   | Ramezankhani et al. 2017 [18] | To determine the environmental factors associated with cutaneous leishmaniasis (CL) | Isfahan province, Iran | From 2010 to 2013 | Spatial analysis, ordinary least square (OLS) regression and geographically weighted regression (GWR) | Climate and environmental factors including temperature, humidity, rainfall, wind speed, normalized difference vegetation index (NDVI), altitude and population density | Five factors including temperature, population density, wind speed, humidity and NDVI had a significant correlation with CL incidence and explained 28.6% of the model | −: Temperature | −: Wind speed |
|     |               |           |       |             |                      |           |              | −: Mean temperature                            | −: Humidity |
|     |               |           |       |             |                      |           |              | −: Mean precipitation maximum wind speed      | −: NDVI |
|     |               |           |       |             |                      |           |              | −: Altitude                                    | |
| 9   | Azimi et al., [11] 2017 | To evaluate the effect of climate factors on the transmission of CL | Khuzestan province, southwestern Iran | 2010-2014 on 4672 cases of CL | Linear regression analysis and autoregression analysis in GIS | Temperature, humidity, rainfall, sunshine hours, evaporation and wind-related climate issues | The number of rainy days, maximum and minimum temperatures and relative humidity are significant variables and predictors of CL incidence and can predict CL incidence | −: Rainy days | −: Sunshine hours |
|     |               |           |       |             |                      |           |              | −: Maximum                                     | −: Evaporation |
|     |               |           |       |             |                      |           |              | −: Temperature                                 | −: Wind speed |
|     |               |           |       |             |                      |           |              | −: Minimum temperature                         | −: Humidity |
| Row | Authors, year | Objective | Place | Sample size | Statistical analysis | Variables | Positive significant variables on CL incidence | Negative/non-significant variables on CL incidence |
|-----|---------------|-----------|-------|-------------|---------------------|-----------|-----------------------------------------------|--------------------------------------------------|
| 10  | Mokhtari et al., 2016 | To investigate the impact of the environmental factors on cutaneous leishmaniasis (CL) prevalence and morbidity | Ilam province, Iran | From 2013 to 2015, on 3237 CL patients | Geographic information system (GIS) and land-use regression (LUR) | Temperature, Population density, Rainfall | Temperature, Urban land use, Agriculture irrigation | Temperature, Land cover, Forest and irrigated lands |
| 11  | Selmane, 2015 | To examine the dynamic relationships between climate factors and the incidence of cutaneous leishmaniasis (CL) | Biskra province, Algeria | From 2000 to 2014, on 2 CL patients | Time series analysis based on the Box-Jenkins method | Mean monthly temperature | Mean temperature of wettest quarter, Temperature at a lag of five months and Relative humidity | Evaporation, precipitation, and wind speed |
| 12  | Chalghaf B, et al., 2016 | To predict the potential distribution of Phlebotomus papatasi and zoonotic cutaneous leishmaniasis caused by leishmania major | Tunisia | 2016, on 1000 CL patients | Grinnellian ecological niche modeling | Rainfall and temperature | Annual precipitation, Mean temperature of wettest quarter, Maximum temperature of warmest month, Grand slope | Rainfall, Soil, Elevation |

*CL: cutaneous leishmaniasis*
| Row | Authors, year       | Objective                                                                 | Place                              | Sample size | Statistical analysis                                                   | Variables                                                                 | Main results                                                                 | Positive significant variables on CL incidence | Negative/non-significant variables on CL incidence |
|-----|---------------------|---------------------------------------------------------------------------|------------------------------------|-------------|------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| 13  | Nikonahad A, 2017 [28] | To investigate the relationship between environmental and meteorological variables and cutaneous leishmaniasis (CL) transmission | Dehloran, located in western Iran  | 2011–2015   | Time series model. Seasonal autocorrelated integrated moving average (SARIMA) model according to the box-jenkins method | Environmental and meteorological variables                             | CL incidence is positively associated with monthly temperature (r=0.77), and earthquakes per month at a lag of 2 months ($\beta$=0.184, p=0.036) and negatively associated with warm days (over than 30°C) at a lag of 2 months ($\beta$=-0.430, p=0.014) | –: Monthly temperature                     | –: Number of warm days (over than 30°C)       |
| 14  | Faraj and lake, 2015 [27] | Relationships between climate variables and CL                             | Asir region, Saudi Arabia          | 1996–2007   | Ordinal logistic analysis                                              | Maximum, mean, and minimum temperature, rainfall, and relative humidity | The temperature was the most important climate variable for the occurrence of CL in the summer and the beginning of autumn. Elevated temperature and rainfall were associated with the increase of CL incidence after 2–4 months | –: Maximum temperature                      | –: Rainfall                                   |
|     |                     |                                                                           |                                    |             |                                                                        |                                                                         |                                                                                |                                |                                |
Rainfall and humidity

In Nikunahd et al.’s study, no significant relationship was found between the annual mean rainfall and CL incidence (p-value = 0.56) [28]. Another study in Saudi Arabia proved the effect of rainfall on CL transmission in the lowlands; hence, it can be argued that rainfall in elevated areas can increase the number of CL cases [27]. Besides, Selmane et al.’s study showed that there was a significant correlation between monthly CL cases and the monthly mean of relative humidity at a lag of zero month (r=0.560) and a lag of 12 months (r=0.582) [17]. In another study, however, the effect of humidity was found to be inverse [18].

Discussion

The results of this review study showed that environmental factors, such as weather conditions and global warming, which lead to the deterioration of the eco-systems, were the most important risk factors for the spreading of CL in the Old World 5. Therefore, weather conditions can act as a non-negligible factor for the fluctuation of leishmaniasis in different countries and regions. According to our results, environmental factors, including weather conditions, temperature, rainfall, precipitation and humidity, can heavily influence the incidence of CL. Temperature is the most important environmental factor that is positively correlated with CL incidence with a lag of 2–5 months. The effect of the time lag of temperature is related to the average incubation period of CL 17. Other studies have also ended up with the same results observing a significant positive correlation between the prevalence of CL and the temperature, such as Ali-Akbarpour et al.’s study in 2012 in different regions of Iran [32] and other countries [26, 31, 33–35] as well as Roger et al.’s study in 2013 in Cayenne, French Guiana, 15 with lags of 4–8 months due to the incubation period of CL. Other studies have reported that an increase in temperature can rise the trend of CL cases [15, 19, 27, 36–39], and the morbidity of the disease starts in March and reaches its peak in July. However, different models and scenarios have demonstrated that the incidence of CL can increase depending on weather conditions in the future years 22.

Based on our findings, the effect of rainfall on CL cases is inconclusive. For example, Faraj’s study reported that rainfall played a role in CL transmission in the lowlands with a lag of 1–3 months [19]. But, in Roger et al.’s study [15], an inverse correlation was observed between the number of annual infections and rainfall (r=−0.71) with a two-month lag and with the number of days and rainfall >50 mm with lags of 4 and 7 months [15]. Nevertheless, Roger et al.’s study showed that a decrease in rainfall was related to a rise in cases after two months [15]. However, the variability of the effects of climate factors may have different impacts on the occurrence of CL depending on the various Leishmania species [11].

The effects of environmental factors on the occurrence of zoonotic cutaneous leishmaniasis (ZCL) were similar to CL incidence in many studies. Yet, the maximum temperature of the warmest quarter, the rainfall in the driest month, the daily average temperature and daily rainfall were the factors affecting the abundance of leishmaniasis vector in the Old World [40]. Moreover, rodent density, average temperature, cumulative rainfall and average relative humidity with different time lags were effective environmental factors having impacts on the ecological condition of Phlebotomus sandflies [41, 42] followed by humidity and precipitation [43]. Another study in Morocco showed a relationship between ZCL incidence and the proportion of rural population [44]. Likewise, other studies reported the co-infection of CL and VL among people and animals as well as negative correlations among normalized difference vegetation index (NDVI) and human density and canine cases [43, 45, 46]. Thus, it can be concluded that leishmaniasis is climate-sensitive, and changes in temperature, rainfall and humidity factors impact its epidemiology because of their effects on population size, distribution and the survival of sandflies [4, 20].

Seid et al.’s study in 2014 in Ethiopia showed that geographical surface, slope, elevation and annual rainfall were the predictors of CL incidence with an overall prediction accuracy of 90.4% [3]. Besides, statistical models including only the temperature and precipitation variables and land-use predictors have demonstrated that such weather-related factors can explain 80% of the variance in the disease patterns whereas land-use factors can only explain 20% of the variance [47]. In Seid et al.’s study, the annual rainfall was the most important, effective climatology variable of CL incidence [3].

Hence, it can be argued that environmental factors had the highest contribution to the distribution of leishmaniasis in the Old World. These factors significantly affected the potential distribution of the main reservoir species [48]. Furthermore, information regarding weather conditions is necessary for the prediction of CL and variation of CL incidence in addition to the data of surveillance systems [17]. However, it can be predicted that because of future weather conditions as a result of the human modification of ecosystems, the incidence of CL will have increased by 35% up to 50% by 2050 [47]. Therefore, weather conditions,
especially temperature and rainfall, should be considered in each region for modeling, disease monitoring and the management of CL incidence in each region. Moreover, GIS modeling methods are useful to facilitate the implementation of evidence-based, integrated disease-control activities.

Nevertheless, this study has some limitations regarding the assessment of relevant studies. Since the majority of CL cases in the Old World were restricted to the arid and semiarid areas of the north, the near east, the Middle East and Central Asia, a high proportion of included studies in this review were from Iran. Also, given the high number of studies focusing on CL, we restricted our results to a narrow time period. Therefore, other review studies with a wider range of studies are suggested for future reviews.

**Conclusion**

The results of this review study revealed that environmental and ecological factors considerably influenced the incidence of CL in the Old World. The local environmental factors, such as weather conditions, temperature and rainfall, can play a key role in the seasonal cycle of CL in a way that most CL cases in the Old World occurred in arid and semiarid areas. Therefore, the change and sequence of local temperature and other environmental factors can change the number of vectors; the number of CL cases can also fluctuate after biological processes in the incubation period. Although dry and warm weather occurring after a rainy season may increase the number of CL cases, wet and cold weather can decrease vector density and lead to a decline in the occurrence of CL during subsequent dry seasons. Finally, it seems that it is impossible to provide a unified strategy for controlling CL incidence in different countries. Thus, apart from educating people to prevent new cases on the one hand and the screening and treatment of patients in endemic areas as a reservoir of the disease on the other, it will be also helpful to consider weather conditions and other environmental factors in control programs. Moreover, according to our results regarding the effect of weather conditions on CL, it seems essential to design an early warning system to predict the incidence of CL based on variations in weather conditions.

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