Review Article

Abolfazl Mohammadbeigi, Salman Khazaei, Hamidreza Heidari, Azadeh Asgarian, Shahram Arsangjang, Abedin Saghafipour, Narges Mohammadsalehi and Hossein Ansari*

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

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.

*Corresponding author: Dr. Hossein Ansari, Health Promotion Research Center, Faculty of Health, Zahedan University of Medical Sciences, Zahedan, Iran, E-mail: ansarih88@gmail.com. https://orcid.org/0000-0003-2755-7864

Abolfazl Mohammadbeigi, Department of Epidemiology and Biostatistics, Neuroscience Research Center, Faculty of Health, Qom University of Medical Sciences, Qom, Iran. https://orcid.org/0000-0002-3142-6413

Salman Khazaei, Research Center for Health Sciences, Hamadan University of Medical Sciences, Hamadan, Iran. https://orcid.org/0000-0001-5918-2310

Hamidreza Heidari, Department of Occupational Health, Research Center for Environmental Pollutants, Faculty of Health, Qom University of Medical Sciences, Qom, Iran. https://orcid.org/0000-0001-6886-1868

Azadeh Asgarian, Izadi Hospital, Qom University of Medical Sciences, Qom, Iran. https://orcid.org/0000-0002-3760-7020

Shahram Arsangjang, Department of Epidemiology and Biostatistics, Faculty of Health, Zanjan University of Medical Sciences, Zanjan, Iran. https://orcid.org/0000-0002-0245-9830

Abedin Saghafipour, Department of Public Health, Research Center for Environmental Pollutants, Faculty of Health, Qom University of Medical Sciences, Qom, Iran. https://orcid.org/0000-0003-3595-6347

Narges Mohammadsalehi, Qom University of Medical Sciences, Qom, Iran. https://orcid.org/0000-0002-2685-4827

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

York, USA), and duplicate records were removed. Based on the conducted search, the titles and abstracts of the searched articles were reviewed and screened for eligibility. The full reviews of the related articles based on titles and abstracts were considered for the final selection. The data describing author, objective, study place, sample size, study type, environmental variables, statistical analysis and the main results were all extracted.

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.

[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 humidifies [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, Sharafi 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].

Temperature

Because of an increase in the temperature at the end of the 21st century, the projection model predicted a 15% rise in the annual number of hospital admissions due to CL compared to 2000 [22]. The effect of high temperature on the incidence of CL was approved in Nikonahad et al.'s study [28]. In another study, Faraj and Lake showed that the most important factor behind CL incidence during summer and the beginning of autumn was the temperature, and an increase in temperature could raise the number of inflicted cases after two-to-four months [27]. Similarly, a strong, significant correlation was reported in Nikonahad et al.'s study between the increase in CL incidence and the monthly temperature (r=0.77; p-value=0.01) [28]. They showed that the number of days per month with a temperature of more than 30 °C had a strong correlation with the increase in CL incidence (r=0.81; p-value=0.01) [28]. Moreover, the survival of adult sandflies in temperatures lower than 15 °C was not reported [31]. The direct effect of temperature was also reported in studies by Ramezankhani et al. [18] and Adegboye et al. in Afghanistan [30], and Ghatee et al. [21] and Artun in Turkey [23]. Moreover, monthly cases were associated with the mean monthly temperature at a lag of five months (r=0.576) and with a monthly accumulated evaporation lag of five months (r=0.513) [17].

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, –: Closeness, proximity to cattle sheds	–: Ground slope –: Elevation
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, –: Mean of evaporation, –: 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 –: Mean of seasonal 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 –: Temperature seasonality	–: Elevation

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
							mersin. The mean diurnal range and mean temperature of the coldest quarter were significantly related to CL incidence in diyarbakir	-: Maximum temperature of the warmest month, -: Mean temperature of the driest quarter mean temperature of the warmest quarter	
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	-: Cold temperature	-: Rainfall
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	-: Mean temperature, -: Relative humidity, -: Slope of the area	-: Maximum wind speed, -: Rainfall, -: Altitude -: Vegetation cover
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	-: Vegetation coverage

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
		topographic factors and CL incidence					speed about 12–16 m/s and an altitude of 600–1,800 m are related to high the incidence of CL	–: Mean temperature –: Mean precipitation maximum wind speed –: Altitude	
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 population density	–: Wind speed –: Humidity –: NDVI
9	Azimi et al., [11] 2017	To evaluate the effect of climate factors on the transmission of CL	Khuzestan province, south-western 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 –: Maximum –: Temperature –: Minimum temperature –: Humidity	–: Sunshine hours –: Evaporation –: Wind speed

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
10	Mokhtari et al., [9] 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), inverse distance weighting (IDW)	17 potentially predictive environmental variables (PPEVs)	A significant relationship was observed between CL incidence and elevation, population, rainfall, temperature, urban land use, poor land, dry farming, and forest and irrigated lands. These variables explained 64% of CL incidence	–: Temperature, –: Urban land use, –: Population density	–: Covering soil –: Rainfall, –: Agricultural irrigation –: Elevation
11	Selmane, 2015 [17]	To examine the dynamic relationships between climate factors and the incidence of cutaneous leishmaniasis (CL)	Biskra province, Algeria from 2000 to 2014		Time series analysis based on the box-jenkins method to fit an autoregressive moving average (ARMA) model	Climate factors	The temperature at a lag of 5 months and relative humidity was a predictive factor of CL incidence. Temperature is a more effective environmental factor with a stronger effect compared to relative humidity	–: Temperature (mean monthly) –: Relative humidity	–: Evaporation, precipitation, and wind speed were non-significant variables
12	Chalghaf B, et al., 2016 [25]	To predict the potential geographic distribution of *Phlebotomus papatasi* and zoonotic cutaneous leishmaniasis caused by leishmania major	Tunisia	2016	Grinnellian ecological niche modeling	Twenty-four environmental layers	Rainfall and temperature are the strongest factors associated with the distribution of sand flies and human cases. Mean temperature of wettest quarter, precipitation of driest quarter maximum temperature of warmest month, and elevation with an 48.2%, 18.6, 15.6, and 10.1% respectively and overall explanation of the variance of 92.5%	–: Mean temperature of wettest quarter –: Precipitation –: Maximum temperature of warmest month –: Elevation	–: Annual precipitation –: Elevation –: Grand slope –: Land cover

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
13	Nikonahad A, 2017 [28]	To investigate the relationship between environmental and metrological variables and cutaneous leishmaniasis (CL) transmission	Dehloran, located in western Iran	2011–2015	Time series model. Seasonal auto-correlated 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 (β=0.184, p=0.036) and negatively associated with warm days (over than 30 °C) at a lag of 2 months (β=−0.430, p=0.014)	–: Monthly temperature; –: Earthquakes per month	–: 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; –: Humidity

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.' 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,
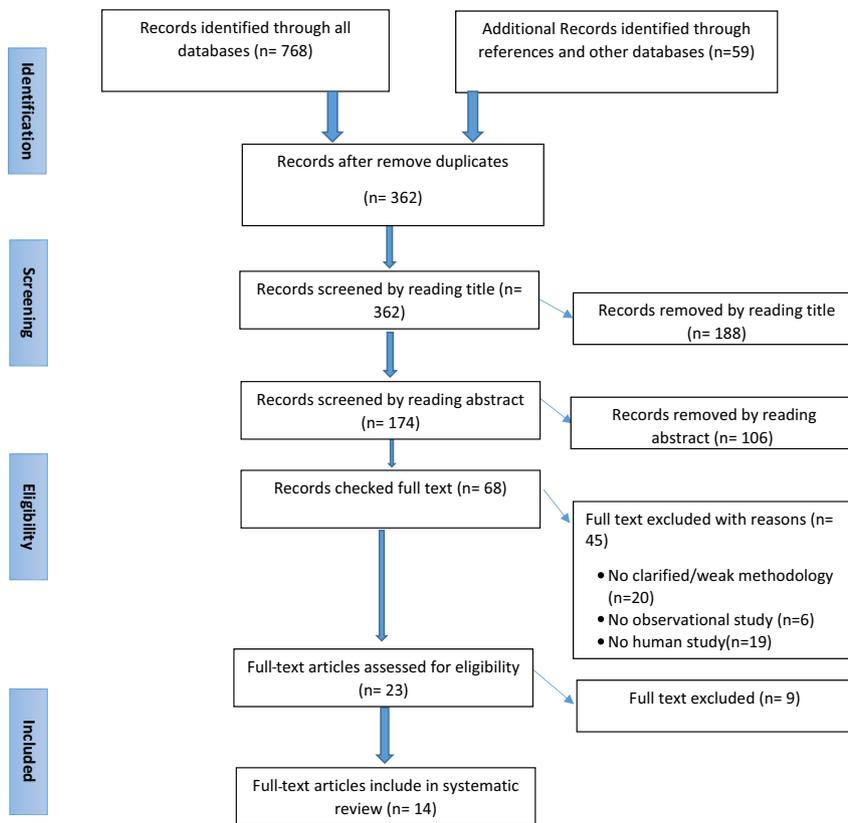
Figure 1: Flow diagram of the study selection for the review process.

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.

Authors Contribution: All authors share similar contributions to the conception or design of the study, the interpretation of the collected data, and the final approval of the article.

Competing interests: The authors declare that they have no conflict of interest.

References

1. Ramezankhani R, Sajjadi N, Nezakati Esmaeilzadeh R, Jozi SA, Shirzadi MR. Climate and environmental factors affecting the incidence of cutaneous leishmaniasis in Isfahan, Iran. Environ Sci Pollut Res Int 2018;25:11516–26.

2. Golpayegani AA, Moslem AR, Akhavan AA, Zeydabadi A, Mahvi AH, Abadi AA. Modeling of environmental factors affecting the prevalence of zoonotic and anthroponotic cutaneous, and zoonotic visceral leishmaniasis in foci of Iran: a remote sensing and GIS-based study. J Arthropod Borne Dis 2018;12:41–66. PMCID: PMC6046107. PMID: 30018993.

3. Seid A, Gadisa E, Tsegaw T, Abera A, Teshome A, Mulugeta A, et al. Risk map for cutaneous leishmaniasis in Ethiopia based on environmental factors as revealed by geographical information systems and statistics. Geospat Health 2014;8:377–87.

4. World Health Organization. Leishmaniasis. 2019. Available from: https://www.who.int/news-room/fact-sheets/detail/leishmaniasis [Accessed 14 August 2019].

5. Inceboz T. Epidemiology and ecology of leishmaniasis. Current topics in neglected tropical diseases. IntechOpen; 2019.

6. Ferreira de Souza RA, Andreoli RV, Toshie Kayano M, Lima Carvalho A. American cutaneous leishmaniasis cases in the metropolitan region of Manaus, Brazil: association with climate variables over time. Geospat Health 2015;10:314.

7. Khazaei S, Mohammadian Hafshejani A, Saatchi M, Salehiniya H, Nematollahi S. Epidemiological aspects of cutaneous leishmaniasis in Iran. Arch Clin Infect Dis 2015;10. https://doi.org/10.5812/archcid.28511.

8. Hartley M - A, Drexler S, Ronet C, Beverley SM, Fasel N. The immunological, environmental, and phylogenetic perpetrators of metastatic leishmaniasis. Trends Parasitol 2014;30:412–22.

9. Mokhtari M, Miri M, Nikoonahad A, Jalilian A, Naserifar R, Ghaffari HR, et al. Cutaneous leishmaniasis prevalence and morbidity based on environmental factors in Ilam, Iran: spatial analysis and land use regression models. Acta Trop 2016;163:90–7.

10. Akhoundi M, Kuhls K, Cannet A, Votýpka J, Marty P, Delaunay P, et al. A historical overview of the classification, evolution, and dispersion of leishmania parasites and sandflies. PLoS Neglected Trop Dis 2016;10. https://doi.org/10.1371/journal.pntd.0004349.

11. Azimi F, Shirian S, Jangjoo S, Ai A, Abbasi T. Impact of climate variability on the occurrence of cutaneous leishmaniasis in Khuzestan Province, southwestern Iran. Geospat Health 2017;12:478.

12. Ramezankhani R, Sajjadi N, Nezakati Esmaeilzadeh R, Jozi SA, Shirzadi MR. Spatial analysis of cutaneous leishmaniasis in an endemic area of Iran based on environmental factors. Geospat Health 2017;12:578.

13. da Costa AP, Costa FB, Soares HS, Tonhosolo R, Augusto Dias R, Ramirez DG, et al. Environmental factors and ecosystems associated with canine visceral leishmaniasis in northeastern Brazil. Vector Borne Zoonotic Dis 2015;15:765–74.

14. de Andrade AR, da Silva BA, Cristaldo G, Ribeiro A, da Cunha Santos M, Andreotti R, et al. Spatial distribution and environmental factors associated to phlebotomine fauna in a border area of transmission of visceral leishmaniasis in Mato Grosso do Sul, Brazil. Parasites Vectors 2014;7:260.

15. Roger A, Nacher M, Hanf M, et al. Climate and leishmaniasis in French Guiana. Am J Trop Med Hyg 2013;89:564–9.

16. Abdullah AYM, Dewan A, Shogib MRI, Rahman MM, Hossain MF. Environmental factors associated with the distribution of visceral leishmaniasis in endemic areas of Bangladesh: modeling the ecological niche. Trop Med Health 2017;45:13.

17. Selmane S. Dynamic relationship between climate factors and the incidence of cutaneous leishmaniasis in Biskra Province in Algeria. Ann Saudi Med 2015;35:445–9.

18. Ramezankhani R, Hosseini A, Sajjadi N, Khoshabi M, Ramezankhani A. Environmental risk factors for the incidence of cutaneous leishmaniasis in an endemic area of Iran: a GIS-based approach. Spat Spatio-temporal Epidemiol 2017;21:57–66.

19. Faraj TK. Influence of climate variables upon selected infectious diseases in Asir Region. Saudi Arabia: School of Environmental Sciences, University of East Anglia; 2011.

20. Gao X, Cao Z. Meteorological conditions, elevation and land cover as predictors for the distribution analysis of visceral leishmaniasis in Sinkiang province, Mainland China. Sci Total Environ 2019;646:1111–6.

21. Ghatee MA, Haghdoost AA, Kooreshnia F, Kanannejad Z, Parisaie Z, Karamian M, et al. Role of environmental, climatic risk factors and livestock animals on the occurrence of cutaneous leishmaniasis in newly emerging focus in Iran. J Infect Public Heal 2018;11:425–33.

22. Mendes CS, Coelho AB, Feres JG, Souza EC, Cunha DA. [The impact of climate change on leishmaniasis in Brazil]. Ciência Saúde Coletiva 2016;21:263–72.

23. Artun O. Ecological niche modeling for the prediction of cutaneous leishmaniasis epidemiology in current and projected future in Adana, Turkey. J Vector Borne Dis 2019;56:127–33.

24. Artun O, Kavur H. A comparison of bioclimatic factors effect for cutaneous leishmaniasis current status between eastern Mediterranean region and Tigris basin of Turkey by using ecological niche modeling. Earth Observ Survey Environ Eng. 2019;VIII:134–41. https://landreclamationjournal.usamv.ro/pdf/2019/Art2019.pdf.

25. Chalghaf B, Chlif S, Mayala B, Ghawar W, Bettaieb J, Harrabi M, et al. Ecological niche modeling for the prediction of the geographic distribution of cutaneous leishmaniasis in Tunisia. Am J Trop Med Hyg 2016;94:844–51.

26. Chavy A, Nava AFD, Luz SLB, Ramírez JD, Herrera G, Demar M, et al. Ecological niche modelling for predicting the risk of cutaneous leishmaniasis in the Neotropical moist forest biome. PLoS Neglected Trop Dis 2019;13. https://doi.org/10.1371/journal.pntd.0007629.

27. Faraj T, Lake IR. The seasonality of cutaneous leishmaniasis in asir region, Saudi Arabia. Int J Environ Sustain 2015;3:1–13. https://www.sciencetarget.com/Journal/index.php/IJES/article/view/519/130.

28. Nikonahad A, Khorshidi A, Ghaffari HR, Miri M, Amarloei A, Mohammadi A, et al. A time series analysis of environmental and metrological factors impact on cutaneous leishmaniasis incidence in an endemic area of Dehloran, Iran. Environ Sci Pollut Res Int 2017;24:14117–23.

29. Sharafi M, Poormotaseri Z, Karimi J, Rezaeian S, Dehghani SL, Afrashteh S. Spatial analysis and geographic factors associated with cutaneous leishmaniasis in southern Iran. J Environ Health Sustain Dev 2020;5:928–34. Available from: http://jehsd.ssu.ac.ir/article-1-213-en.html.

30. Adegboye MA, Olumoh J, Saffary T, Elfaki F, Adegboye OA. Effects of time-lagged meteorological variables on attributable risk of leishmaniasis in central region of Afghanistan. Sci Total Environ 2019;685:533–41.

31. Guzmán H, Tesh RB. Effects of temperature and diet on the growth and longevity of phlebotomine sand flies. Biomedica 2000;20: 190–9.

32. Ali-Akbarpour M, Mohammadbeigi A, Tabatabaee SHR, Hatam G, surgery A. Spatial analysis of eco-environmental risk factors of cutaneous leishmaniasis in southern Iran. J Cutan Aesthetic Surg 2012;5:30–5.

33. Fischer D, Thomas SM, Beierkuhnlein C. Temperature-derived potential for the establishment of phlebotomine sandflies and visceral leishmaniasis in Germany. Geospat Health 2010;5: 59–69.

34. Quinonez-Diaz L, Mancilla-Ramirez J, Avila-Garcia M, Berron A, González S, Paredes Y, et al. Effect of ambient temperature on the clinical manifestations of experimental diffuse cutaneous leishmaniasis in a rodent model. Vector Borne Zoonotic Dis 2012; 12:851–60.

35. Gama Ker H, Dian de Oliveira Aguiar-Soares R, Mendes Roatt B, Carneiro CM, Teixeira-Carvalho A, Martins-Filho OA, et al. Effect of the preservative and temperature conditions on the stability of *Leishmania infantum* promastigotes antigens applied in a flow cytometry diagnostic method for canine visceral leishmaniasis. Diagn Microbiol Infect Dis 2013;76:470–6.

36. Chretien J-P, Anyamba A, Small J, Britch S, Sanchez JL, Halbach AC, et al. Global climate anomalies and potential infectious disease risks: 2014-2015. PLoS Curr 2015;7. https://doi.org/10.1371/currents.outbreaks.1395fbc1374a1378fb4695e1049baabfc1372fc8289f.

37. Garni R, Tran A, Guis H, Baldet T, Benallal K, Boubidi S, et al. Remote sensing, land cover changes, and vector-borne diseases: use of high spatial resolution satellite imagery to map the risk of occurrence of cutaneous leishmaniasis in Ghardaia, Algeria. Infect Genet Evol 2014;28:725–34.

38. Karagiannis-Voules D-A, Scholte RG, Guimaraes LH, Utzinger J, Vounatsou P. Bayesian geostatistical modeling of leishmaniasis incidence in Brazil. PLoS Neglected Trop Dis 2013;7. https://doi.org/10.1371/journal.pntd.0002213.

39. Lewnard JA, Jirmanus L, Júnior NN, Machado PR, Glesby MJ, Ko AI, et al. Forecasting temporal dynamics of cutaneous leishmaniasis in northeast Brazil. PLoS Neglected Trop Dis 2014;8. https://doi.org/10.1371/journal.pntd.0003283.

40. Gao X, Huang Y, Zheng J, Xiao J, Wang H. Impact of meteorological and geographical factors on the distribution of *Phlebotomus chinensis* in northwestern mainland China. Med Vet Entomol 2020;76:365–71.

41. Talmoudi K, Bellali H, Ben-Alaya N, Saez M, Malouche D, Chahed MK. Modeling zoonotic cutaneous leishmaniasis incidence in central Tunisia from 2009-2015: forecasting models using climate variables as predictors. PLoS Neglected Trop Dis 2017;11. https://doi.org/10.1371/journal.pntd.0005844.

42. Zareichaghabaleki Z, Yarahmadi D, Karampour M, Shamsipour A. [Spatial dynamics of Phlebotomus sand-fly ecological condition in response to climate change]. Feyz J Kashan Univ Med Sci 2019; 23:158–67. [Fultext in Persian].

43. Jahanifard E, Hanafi-Bojd AA, Nasiri H, Charrahy Z, Abai MR, Yaghoobi-Ershadi MR, et al. Prone regions of zoonotic cutaneous leishmaniasis in southwest of Iran: combination of hierarchical decision model (AHP) and GIS. J Arthropod Borne Dis 2019;13: 310–23. PMID: 31879670.

44. Kahime K, Boussaa S, Idrissi AL - E, Nhammi H, Boumezzough A. Epidemiological study on acute cutaneous leishmaniasis in Morocco. J Acute Dis 2016;5:41–5.

45. Ursine RL, Dias JV, Morais HA, Pires HH. Human and canine visceral leishmaniasis in an emerging focus in Aracuai, Minas Gerais: spatial distribution and socio-environmental factors. Mem Inst Oswaldo Cruz 2016;111:505–11.

46. Figueiredo ABF, Werneck GL, Cruz M, Silva JPD, Almeida AS. Land use, land cover, and prevalence of canine visceral leishmaniasis in Teresina, Piaui State, Brazil: an approach using orbital remote sensing. Cad Saúde Pública 2017;33. https://doi.org/10.1590/0102-311x00093516.

47. Purse BV, Masante D, Golding N, Pigott D, Day JC, Ibañez-Bernal S, et al. How will climate change pathways and mitigation options alter incidence of vector-borne diseases? A framework for leishmaniasis in South and Meso-America. PLoS One 2017;12. https://doi.org/10.1371/journal.pone.0183583.

48. Gholamrezaei M, Mohebali M, Hanafi-Bojd AA, Sedaghat MM, Shirzadi MR. Ecological niche modeling of main reservoir hosts of zoonotic cutaneous leishmaniasis in Iran. Acta Trop 2016;160: 44–52.