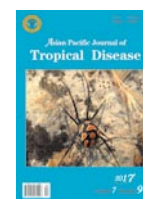


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## The burden of leishmaniasis in Iran, acquired from the global burden of disease during 1990–2010

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## ABSTRACT

**Objective:** To report and measure the burden of leishmaniasis in Iran using the global burden of disease (GBD) results, conducted by the Institute for Health Metrics and Evaluation for the years 1990 to 2010, and provide some recommendations for reaching better conclusions about the burden of disease.

**Methods:** GBD burden and fatality rates of leishmaniasis were compared with the findings registered by the Ministry of Health and Medical Education (MOHME). Data obtained from the GBD for the years 1990 to 2010 were used to estimate the disability-adjusted life-years and fatality rates of leishmaniasis in Iran.

**Results:** The GBD estimated 229 714 disability-adjusted life-years due to leishmaniasis in Iranian people of all ages and both sexes. The number of deaths caused by visceral leishmaniasis (VL) had decreased significantly in recent years. MOHME registered data on fewer than 30 deaths in Iran from 1990 to 2010.

**Conclusions:** The underreporting of VL deaths is always more pronounced. Findings indicate that the GBD estimation of mortality rates was surprisingly higher than MOHME's data. The burden of leishmaniasis decreased significantly between the years 1990 and 2010 in both data sources. The possible explanation for this decrease has been discovered through the establishment of a VL surveillance system in various parts of Iran, particularly in endemic areas.

## 1. Introduction

Leishmaniasis is a vector-borne parasitic disease caused by the obligate intracellular protozoan parasite *Leishmania* spp.[1,2]. Based on World Health Organization reports and others, leishmaniasis is classified as a neglected tropical disease[3-5]; among all tropical

diseases, leishmaniasis is ranked the second in mortality and the fourth in morbidity[6-9]. Leishmaniasis is estimated to cause the ninth largest disease burden among individual infectious diseases; however, as a tropical disease, it has been largely overlooked in the discussion of priorities[1]. Visceral leishmaniasis (VL) evidence from different countries suggests that the burden of disease is increasing[10]. Moreover, it shows that epidemiological features and determinants of VL outbreaks are changing not only around the Mediterranean basin, but also in other endemic areas of the world because of environmental changes, immunosuppression and drug resistance[11].

Iran is one of the main endemic foci of leishmaniasis and has various clinical manifestations of the disease (Figure 1)[4]. The most common form is related to cutaneous leishmaniasis (CL).

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CL is dispersed in more than half of the Iranian provinces (20 out of 31), with prevalence rates ranging from 1.8% to 37.9%[7,12]. Alvar *et al.* showed that from 2004 to 2008, the number of reported CL cases/year and an estimated annual number of new CL cases were 26630 to 113300, respectively, while VL was responsible for 149 reported cases/year and an estimated 300–600 new VL cases annually. In addition, VL was fatal in almost all untreated cases[1,13]. More recently, Mohebbali showed that through the end of 1993, approximately 4300 cases of VL were diagnosed in different parts of Iran. More than 2000 cases of VL were diagnosed in 31 provinces of Iran prior to 2012[14]. Sporadic cases of post kala-azar dermal leishmaniasis and muco-cutaneous leishmaniasis were also reported in the country[15,16]. Furthermore, several studies have shown that VL is an opportunistic disease in AIDS patients in Iran[14,17].

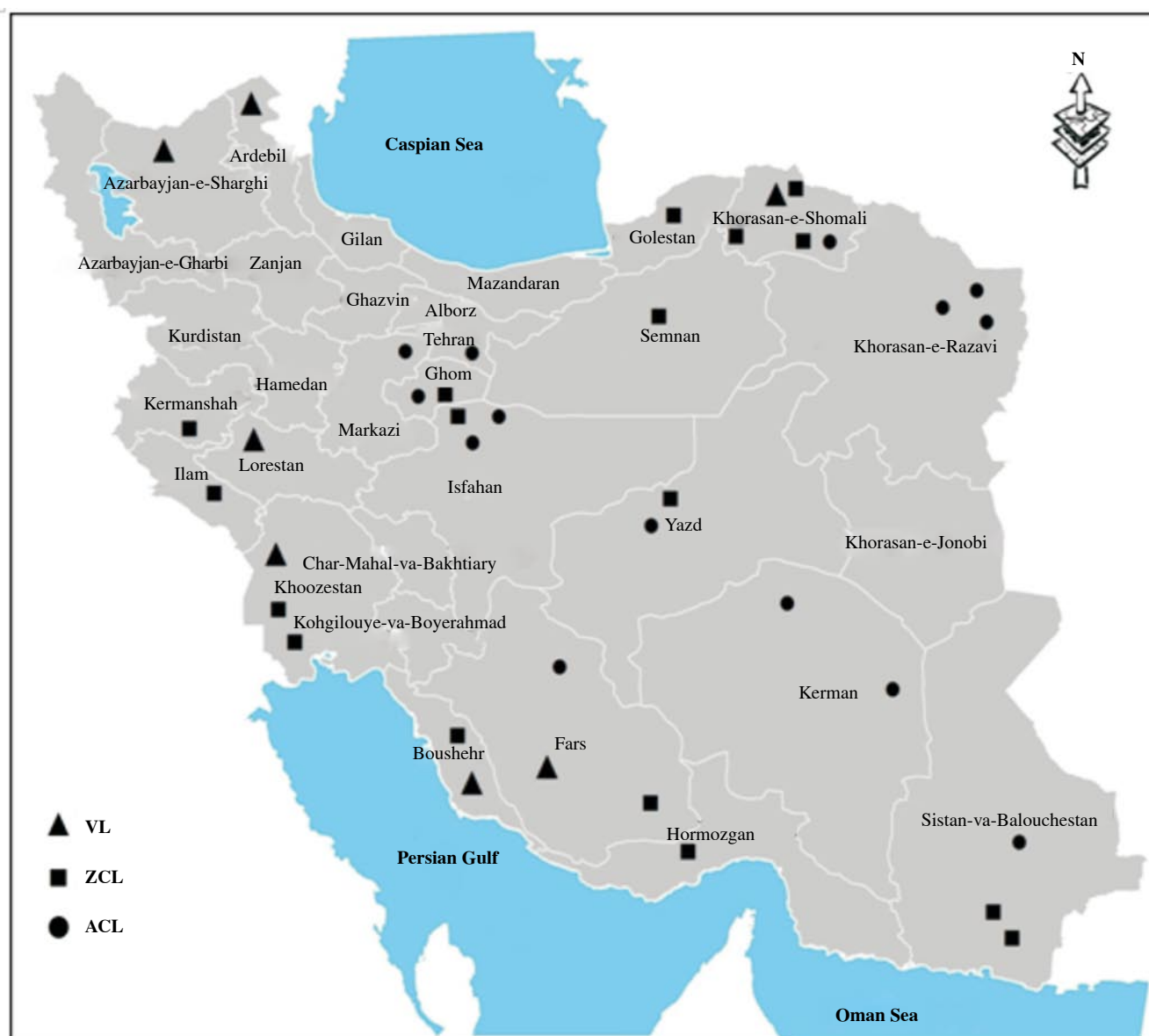
Since a few decades ago, Iran has achieved remarkable success in improving health[18]. Between 1990 to 2010, life expectancy has increased from 64.6 to 71.6 years for males, and from 71.0 to 77.8 years for females, respectively[8,19]. Leishmaniasis remains a major health problem in different parts of Iran, with the increased concerns in recent years[20]. Therefore, the measurement of health metrics,

including disability and a death rate, in an at-risk population, using well-known criteria is indispensable[21].

Global burden of disease (GBD) methodology is a systematic effort to present the best estimates of incidence and prevalence and as well as global assessments of mortality, morbidity, and disability resulting from major diseases, injuries, and risk factors[22,23]. The authors believe that the burden of leishmaniasis has been seriously underestimated in Iran, and that its epidemiology has not been widely verified. Few reports are known about the burden of leishmaniasis in the general population[14,24]. This report describes the burden of leishmaniasis in Iran from 1990 to 2010 and introduces the GBD method, which has recently been developed by the Institute for Health Metrics and Evaluation. Additionally, VL mortality rates from the GBD were compared with Iran's death registration figures.

## 2. Materials and methods

In the current survey, we used the data of the GBD 2010 study that includes 291 diseases and injuries in 20 age groups and both



**Figure 1.** High-endemic foci of leishmaniasis in Iran.

VL is caused by *Leishmania infantum*; ZCL: Zoonotic cutaneous leishmaniasis (caused by *Leishmania major*); ACL: Anthroponotic cutaneous leishmaniasis (caused by *Leishmania tropica*) (created by ArcGIS version 10.2).

sexes[25]. The full and precisely detailed explanation of data, modeling strategies, estimation, and evaluation for GBD have been reported in detail elsewhere[22,26-30]. In the GBD 2010 study, numerous criteria were used to describe the outcomes of health loss related to specific causes of disease and/or injury, including death rates, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life years (DALYs)[31]. YLL was calculated via multiplying the number of deaths (N) in each age group by a reference life expectancy (LE) at the age of death (d) using the following formula:

$$YLLs = N \times (LE - d)$$

YLD was calculated via multiplying the incident cases (I) by the disability weight (DW) and the duration of illness (D):

$$YLDs = I \times D \times DW$$

DW was scaled from 0 to 1 with 0 implying full health and a value of 1 being equivalent to death. It was measured for 220 unique health conditions in the GBD 2010 study that covered 1160 diseases and injuries[26,32]. The procedure for adjusting the years of healthy life lost is termed disability adjustment and is expressed as DALYs. DALYs is a measure of overall disease burden which is expressed as the number of years lost due to ill-health, disability, or early death. Therefore, DALYs was calculated by the sum total of YLLs and YLDs for each disease outcome, age, and sex:

$$DALYs = YLLs + YLDs$$

The level of uncertainty for each cause-specific DALY was calculated by combining uncertain levels of all-cause mortality, cause-specific mortality, prevalence, and DW[22,33].

The estimates for most diseases were collected from a database covering all age-sex-country year groups and using a Bayesian meta-regression method established for the GBD 2010 study (DisMod-MR)[34]. The GBD 2010 study made an estimation for each disease through a systematic analysis of published and accessible unpublished data sources on incidence, prevalence, remission, and mortality[31,35]. Causes of death were measured by utilizing a detailed database of vital registration, verbal autopsy, surveillance, and other sources covering nearly 187 countries from 1990 to 2010[22]. Globally, the cause of death ensemble modeling was used for all causes of death[29]. Leishmaniasis was one of the most considerable items within the infectious diseases category that were measured using DALYs in GBD. Death rates and incidence of leishmaniasis in Iran were taken from Iran's death registration system of the Ministry of Health. Statistically, the collected data were analyzed by using GraphPad Prism 5 software.

### 3. Results

In the current study, we used the GBD 2010 data set to report significant findings for the burden of leishmaniasis (DALYs) in Iran (Figure 1), the burden of mortality due to premature deaths (YLL), and the burden of disability due to nonfatal health outcomes (YLD) along with disease death rates.

#### 3.1. Leading causes of DALYs

The detailed comparison of DALYs and death rates per 100000 leishmaniasis cases in the period 1990 to 2010 and classified by age and sex are provided in Table 1. Regardless of differences in gender, the burden of leishmaniasis resulting in death and/or disability was estimated to be a total of 229714 DALYs from 1990 to 2010, comprised of 12123 YLDs and 217591 YLL, respectively. Rates per 100000 people were calculated as 371 for DALYs, 352 for YLD, and 19 for YLL (Figure 2), respectively.

#### 3.2. Sex and age patterns for DALYs

The burden of DALYs was lower for females (31.3%) than for males (68.7%) (Figures 3 and 4); 34.4% of YLLs and 49.3% of YLDs were in females, while 69.6% of YLLs and 50.7% of YLDs were in males. DALY rates per 100000 were 507.16 years for males and 232.06 years for females, respectively. YLL rates were 487.55 years per 100000 males and 212.84 years per 100000 females. YLD rates were 19.75 and 19.20 years per 100000 people for males and females, respectively. The burden of premature death was higher in males than in females, but the burden of disability was almost the same in both, which resulted in more burden of disease and death altogether for males than did for females (Figures 3 and 4).

The highest burden of disability was in females aged 70 years and above in 1990. The highest burden of death was in males in the under 5-year age groups in 1990. Age patterns of deaths and YLL were nearly similar: the number of deaths decreased with age, and the burden of death (YLL) was greater for children (Figures 3 and 5).

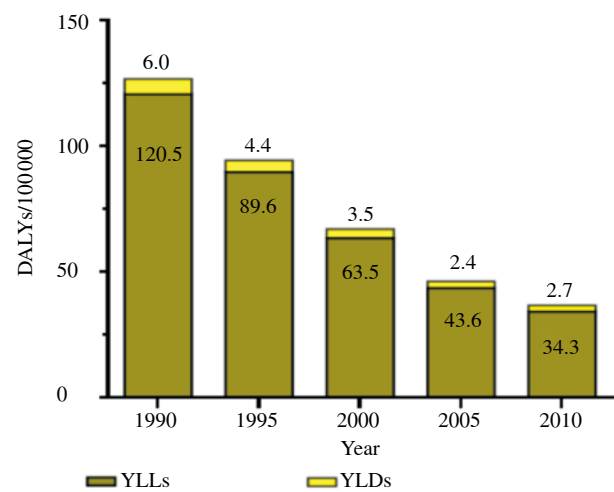


Figure 2. Total YLD and YLL rates per 100000 of leishmaniasis in Iran (1990 to 2010).

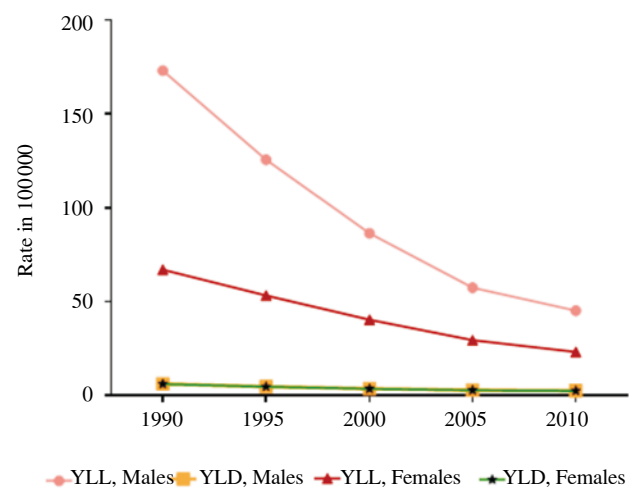


Figure 3. Sex differentials in burden of leishmaniasis by years in Iran (1990 to 2010).

Figure 5 summarizes the DALYs of leishmaniasis in Iran from 1990 to 2010 in different age groups. Our findings indicated that the minimum and maximum rates of DALYs between 1990 and 2010 were related to the ages of > 70 and under 5 in 1990, respectively. After 2000, however, the highest rate of DALYs was in the 15–49

**Table 1**

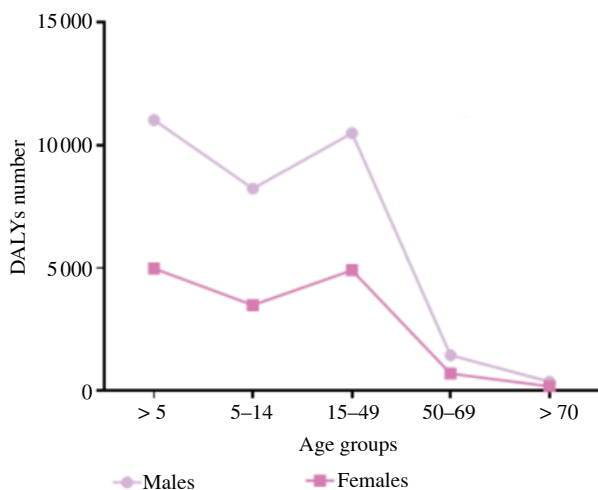
DALYs and death rates per 100000 attributable to leishmaniasis by all ages and both sexes in Iran (1990 to 2010).

Age groups	Sex	DALY/100 000					Death/100 000				
		1990	1995	2000	2005	2010	1990	1995	2000	2005	2010
< 5 years	Male	501.567	372.791	246.278	149.907	131.545	5.906	4.384	2.886	1.745	1.526
	Female	201.473	164.922	128.202	102.287	88.377	2.360	1.926	1.490	1.182	1.018
	Both	354.829	271.158	188.555	126.630	110.447	4.172	3.182	2.204	1.469	1.278
5–14 years	Male	149.579	125.468	102.324	81.953	66.817	1.899	1.598	1.309	1.050	0.850
	Female	63.665	55.419	47.217	38.065	31.204	0.782	0.685	0.587	0.473	0.383
	Both	107.775	91.280	75.389	60.563	49.458	1.355	1.153	0.956	0.769	0.622
15–49 years	Male	102.143	80.915	63.883	45.957	35.633	1.619	1.292	1.016	0.727	0.572
	Female	40.626	36.528	31.373	23.582	18.346	0.574	0.541	0.476	0.358	0.280
	Both	71.018	58.497	47.594	34.938	27.097	1.090	0.913	0.745	0.545	0.428
50–69 years	Male	64.233	56.920	48.662	38.058	32.403	1.871	1.773	1.564	1.230	1.028
	Female	34.325	28.720	23.764	17.923	15.068	0.784	0.741	0.658	0.508	0.422
	Both	49.761	43.046	36.174	28.011	23.718	1.345	1.265	1.110	0.870	0.724
> 70 years	Male	60.143	52.934	44.093	34.418	28.649	3.645	3.328	2.956	2.414	2.116
	Female	32.525	28.487	24.725	20.089	16.879	1.575	1.552	1.514	1.348	1.180
	Both	46.645	41.313	34.867	27.794	23.111	2.633	2.483	2.269	1.921	1.676
All ages	Male	179.269	130.322	89.996	60.150	47.628	2.484	1.883	1.379	0.981	0.803
	Female	72.967	57.774	43.823	32.125	25.535	0.963	0.800	0.645	0.494	0.403
	Both	126.628	94.326	67.088	46.393	36.748	1.731	1.346	1.015	0.742	0.606

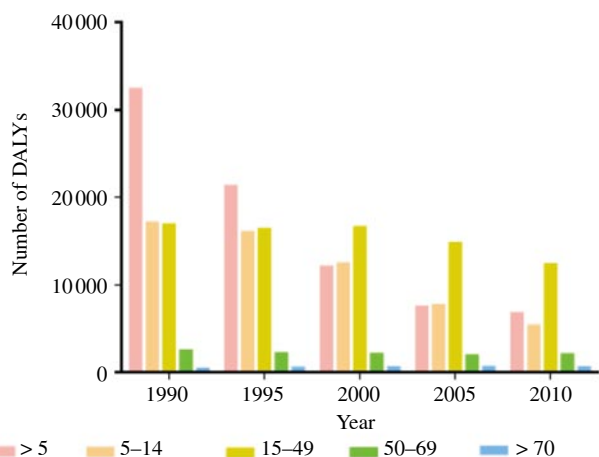
years age group. The DALYs rate in the age group 15–49 years was almost equal in all 20 years of study. Females had a lower DALY rate than males in all age groups (Table 1).

**3.3. Death and fatality rates**

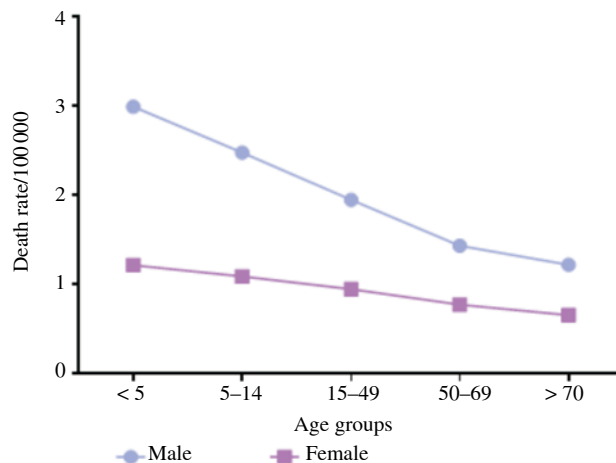
Based on the statistics from the GBD 2010 study, 3391 people died in Iran due to leishmaniasis between the years 1990 to 2010, causing a rate of 217 591 YLLs (97.7% of total DALYs). In Table 1, the section of death rate/100 000 demonstrated a detailed comparative view of deaths per 100 000. The data showed that the death rate due to leishmaniasis in all ages and sexes decreased by 55%, which was a significant change. The highest death rate was observed in 1990 in the under-5 age group with 5.906 per 100 000 in males, and the lowest rate was in 2010 in the 50–69 years age group with 0.422 per 100 000 in females. Table 1 presents the higher prevalence of leishmaniasis in males at all studied ages (Figure 6).



**Figure 4.** DALY numbers of VL in different age groups by sex in Iran (1990 to 2010).



**Figure 5.** DALY numbers of leishmaniasis by age in Iran (1990 to 2010).



**Figure 6.** Death rates per 100 000 of VL in different age groups by sex in Iran (1999 to 2010).

Data obtained from the GBD 2010 study showed that the highest (949) and lowest (448) numbers of deaths were determined to be between 1990 and 2010, respectively, among all age groups. The rate of death in the 15–49 years age group from 1990 to 2010 did not change considerably. Surprisingly, death rates were higher in males at all ages. Moreover, the number of deaths gradually decreased with age (Figure 6). According to Iran’s death registration system of the Ministry of Health and Medical Education (MOHME), less than 30 deaths in Iran were caused by VL between 1990 and 2010

(unpublished data).

#### 4. Discussion

The development of a singular concise measure of population health, namely DALYs or burden of disease, has greatly simplified scientific and political assessments of the comparative significance of disparate diseases, injuries, and risk factors, especially for priority setting in the health care sector. The current study represents the first effort to calculate DALYs and the burden of leishmaniasis in Iran using GBD methodology in the period of 1990–2010 across all age groups and both sexes and compared with MOHME data.

Causes of death were determined from a comprehensive database of verbal autopsy, vital registration, and surveillance data and other sources covering 187 countries from 1990 to 2010 (Salomon *et al.*[19]). For all causes of death except HIV, the global team used the cause of death ensemble model[29]. Leishmaniasis was one of the most important diseases in the infectious diseases category estimated in GBD by DALYs[22].

Our survey results indicated that during the 20-year period (1990–2010), DALYs and death rates of leishmaniasis in Iran diminished considerably; these results agree with the findings of a survey by Yang *et al.* in China[31]. According to Mohebbi *et al.*, the incidence of VL has also decreased in Iran, and the number of deaths from leishmaniasis is gradually decreasing[14,36]. Similarly, the burden of this disease in Iran declined between the years 1990 and 2010. MOHME data showed that the annual incidence of kala-azar decreased considerably from 1.88 to 0.77 per 1000 children between 1985 and 2000[36]. A very recent study showed that the burden of leishmaniasis in Iran is lower than the GBD 2010 study[37].

Analysis indicated infection rates were higher in males than females, probably due to the fact that in Iran, males usually work in the fields, and consequently, they are directly exposed to biting of sandflies, while females cover their bodies with the hijab[38]. The under-5 year group had higher infection rates than the other groups[14,39]. The mechanism of action that results in this higher incidence of leishmaniasis among children is poorly understood. One previous study revealed low immunity responses of Th1 (premunition/concomitant deficiency) to *Leishmania* parasites in this age group[39]. An animal model study performed by Muller *et al.* suggests that high arginase activity in younger mice can promote lesion pathology and parasite burdens in comparison to older mice[40].

In general, a number of surveys have measured the burden of leishmaniasis in China and other countries[22,28,29,31]. The results of the current study are in accordance with the outcomes of previous studies performed by Murray *et al.* and Lim *et al.* and support those findings made by Yang *et al.*[22,28,31]. Lozano *et al.* confirmed that the number of deaths caused by neglected tropical diseases like leishmaniasis had decreased globally[29]. The decrease in the burden of leishmaniasis during the 20-year period under study may be due to several factors, such as health promotion, climate changes, diet supplement, host immunity, and host genetics[31].

Accurately estimating the burden of leishmaniasis is challenging, because of various clinical features, epidemiological diversity, the lack of reliable data on incidence, prevalence, and duration, and various disease syndromes. Almost half of the population in endemic foci may have an asymptomatic leishmanial infection. The contribution of such individuals to transmission is probably less than that for active kala-azar, but this cannot usually be known. A passive surveillance system cannot recognize all leishmaniasis cases, and the disease is noticeable in some endemic and non-endemic areas. Underreporting is likely to vary greatly based on distance to health

care, availability of private providers and of antileishmanial drugs, the presence of research groups, and local awareness of the disease.

It should be noted that, although the GBD study is important and valuable in determining the burden of diseases all around the world, it has some limitations. One of the limitations in the current survey is that the burden of leishmaniasis has not been measured at a sub-national level in Iran. Another noteworthy limitation of the present study is that the GBD study did not distinguish between the burden of CL and VL in Iran. This may be a consideration for future studies because CL and VL are endemic diseases in Iran, and each has its own burden of disease and fatality rate. However, due to the lack of data, we did not estimate post kala-azar dermal leishmaniasis, muco-cutaneous leishmaniasis, and other less frequent forms of leishmaniasis in this study.

In this study, our GBD-based analyses have demonstrated a gradually decline in the burden of leishmaniasis in Iran over the last two decades. The outcome of this survey may aid policy makers in determining what factors can eradicate the burden of disease in Iran. Moreover, the health sector can be benefited through monitoring and surveillance strategies. Therefore, the uncertainties in the data of this report will spur activities to develop an evidence base for leishmaniasis and other neglected diseases. Given that the death rate and burden of leishmaniasis estimated by GBD were much higher than that assessed by MOHME, it is suggested that in order to accurate estimation of GBD, the all missing VL and CL cases should be comprehensively considered in all endemic foci of Iran by MOHME's experts in the future investigations.

#### Conflict of interest statement

We declare that we have no conflict of interest.

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