

## Adamantiades-Behçet's Disease: Demographic and clinical comparison between Iranian and multinational German populations

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Adamantiades-Behçet's disease (ABD) is a chronic, recurrent inflammatory disease with an unclear aetiology. Major and minor clinical signs characterize ABD. Major signs generally comprise oral and genital aphthae and skin and eye manifestations. Minor signs include joint, neurological, and gastrointestinal symptoms and vascular involvement. This work aims to compare the prevalence and clinical manifestations of ABD using available study results from Iran and Germany. This report is based on statistical data from Iran and Germany. A long-term study over 35 years from the Rheumatology Research Center, Shariati Hospital, Tehran University of Medical Sciences, and a large German epidemiological study dealing with data from the German Registry for ABD and data on the disease in Europe are the information sources. Additionally, data from recent ABD studies listed in PubMed are used. Although the prevalence of ABD in Iran, with 80 patients per 100,000 inhabitants, is markedly higher than in Germany, with 4.2 patients per 100,000 inhabitants, the male-to-female ratio and age of onset are similar in the two populations. In Iran, the male-to-female ratio is 1.3:1, and the average onset age is  $26 \pm 11.3$  years. In Germany, the male-to-female ratio is 1.4:1, and the average onset age is  $27.7 \pm 11.6$  years. The incidence of the disease is decreasing, both in Iran and other parts of the world. Recurrent oral aphthae were the most common onset manifestation in patients of both Iran (82.7%) and Germany (84.5%), with ocular manifestations more common onset signs in Iran (8.7%) than in Germany (5.1%). Except for recurrent genital ulcers, which were more common in women in both countries, all other clinical signs – except oral aphthae – were more common in male patients in both countries. Minor clinical signs differed. A markedly different prevalence was observed in the study populations of Iran and Germany, with the disease being more common in Iran. However, despite the different origins, demographics and major clinical signs of ABD were similar in both countries. ABD is most frequently detected in young patients.

**Keywords:** Adamantiades-Behçet's disease; epidemiology; clinical signs, Iran; Germany

### Introduction

Adamantiades-Behçet's disease (ABD) is a chronic inflammatory disease with characteristic clinical symptoms and an unclear aetiology. According to the general viewpoint, it is a vascular disease. Epidemiological studies have confirmed that environmental factors act as triggers in genetically

susceptible patients, and microbial agents are the main environmental factors [1-3]. The geographic area of ABD distribution is mostly from 30°–45° north latitude. This corresponds to the course of the ancient Silk Road, which led from China via the Far East and the Mediterranean countries to Europe. Because of this epidemiological aspect,

ABD has also been called "Silk Road disease" [4,5]. Iran is located on the ancient Silk Road and is considered among the countries with the highest ABD prevalence worldwide. Historians say the high prevalence of ABD in Iran is due to Turkic tribes from China. This is due to the associated genetic mixing of Iran's immigrant and indigenous populations [5,6]. Turkey, with up to 420 cases per 100,000 inhabitants [7], exhibits the highest ABD prevalence in the world. Iran stands at 68–80 cases per 100,000 [7,8] after Turkey, Israel with 146 per 100,000 [9], and China with 110 cases per 100,000 inhabitants [10], in the fourth place. As a result of globalization, incidence and prevalence rates in Western industrialized countries, including Germany, have increased due

to Asian and South-eastern European immigration. As a result, physicians in Europe are increasingly confronted with ABD [1,11]. Germany's nationwide prevalence of ABD is 0.9 per 100,000 inhabitants [11]. Conversely, Berlin, as a city with one of the largest Turkish communities in Germany and a high proportion of migrants, has a prevalence of 1.47 per 100,000 inhabitants [12]. The clinical diagnosis of the disease is made according to the criteria of the "International Team for the Revision of the International Criteria for Behçet's Disease (ICBD)" (Table 1) [13]. Therapy is carried out according to international standards, mainly with corticosteroids, often in combination with immunosuppressants, depending on the organ(s) involved and the patient's condition [14, 15].

**Table 1:** Revised International criteria for the diagnosis of ABD

Symptom	Adults	Children ≤16**
	Points	Points
Ocular lesions	2	1
Recurrent genital aphthous ulcers	2	1
Recurrent oral aphthae	2	1
Recurrent skin lesions	1	1
Neurological manifestation	1	1
Vascular manifestation	1	1
Positive pathergy test <sup>o</sup>	1	---

\* ≥ 4 points are considered a definite diagnosis in adults. <sup>o</sup> A positive pathergy test is optional.

\*\* ≥ 3 points are considered a safe diagnosis in children.

ABD in Iran was first reported in 1975 in the Rheumatology Department of Shariati University Hospital under the supervision of Professor Fereydon Devatchi. This department of Shariati University Hospital was renamed the Rheumatology Research Center (RRC) in 1981 [7,16,17]. In 1990, the Deutsches Register Morbus Adamantiades-Behçet (DR-MAB) was founded under Prof. Dr. Christos Zouboulis' presidency in the Department of Dermatology, University Hospital Benjamin Franklin, Freie Universität Berlin [1]. Since November 2005, Staedtisches Klinikum Dessau has been the DR-MAB administrative headquarters. This organization currently coordinates the cooperation of over 30 medical departments in Germany on this topic [4,11]. For different reasons, Iran and Germany have developed over the years well-organized clinical registries on ABD with their standardized questionnaire. This study compared clinical data from these two registries.

## Material and Methods

In this study, the patient data and the frequencies of recorded clinical symptoms were documented using the standardized questionnaire in the participating centers. From 1975 to October 2014, 7,187 patients from all over Iran were referred to the ABD center of the RRC of the Tehran University of Medical Sciences as part of a longitudinal study. This study from 2016 [7] shows that 6,075 patients were older than 16 years, of which 3,403 (56.0%) were male and 2,671 (44.0%) were female. A multidisciplinary team diagnosed rheumatology, dermatology, and ophthalmology specialists. Specific classifications or diagnostic criteria were not considered for diagnosis. Nonetheless, 96.8% of the patients met the ICBD [13]. One hundred and five items were systematically examined for each patient in the registry [7]. In the 2016 analysis, the statistical analysis included a 95% confidence interval (CI), a standard deviation (SD)

(SD) for the mean, and the percentages for each item [7]. Since establishing the DR-MAB in 1990 in the Department of Dermatology, University Hospital Benjamin Franklin, the Free University of Berlin until October 1997, 218 patients with ABD have been registered. Of these, 130 (59.6%) were male and 88 (40.4%) were female. This cohort included 89 (40.8%) German-origin patients, 100 (45.9%) of Turkish origin, and 29 (13.3%) of other origins. Of these patients, 196 met the RICBD [13]. By 2015, 747 patients were recorded in this registry [12]. Of the 747 patients, 434 (58.1%) were male and 313 (41.9%) were female [12]. The statistical methods of the German study from 1997 were described as follows: Data are presented either as median values with minimum and maximum values shown in brackets or as mean values  $\pm$  one standard deviation. The Wilcoxon performed statistical comparisons matched pairs test, Mann-

Whitney-U test, or Kruskal-Wallis test. A chi-square test or two-tailed exact Fisher test compared clinical findings frequencies. Differences were defined as statistically significant at  $P < 0.05$  [1]. This article utilizes patient data collected from both ABD registries. This paper is a systematic descriptive study of the literature from 1995 to 2017 and compares ABD studies from Germany and Iran. A systematic literature search was performed on Medline's electronic biomedical database via PubMed.

## Results

### Demographic data

The COPCORD study reported a prevalence of 80 per 100,000 inhabitants in Iran in 2016 [7] (Table 2). In Germany, a prevalence of 0.9 per 100,000 inhabitants was reported in 2012 [11], but a new study reported a prevalence of 4.2 per 100,000 inhabitants in 2015 [12] (Table 2). In

**Table 2:** Prevalence of ABD in Iran and Germany

Country	Year	Prevalence per 100,000 inhabitants
Iran	2005	16.7 *
Iran	2016	80**
Germany	2012	0.9
Germany	2015	4.2

\* hospital based referral patients

\*\* community base population.

2016, out of the 6075 patients in Iran, 3403 (56%) were male and 2671 (44%) were female [7]. The male-to-female ratio was 1.3, and the average onset age was 28.3 years for both sexes. Until 2012, the DR-MAB had 721 patients registered in Germany, of whom 35.8% were of German origin, and 42.7% were of Turkish origin; among them, 422 were male (58.5%) and 299 female (41.5%) [11]. For the population of Turkish origin in Berlin, the prevalence of 77.4 per 100,000 inhabitants was similar to that of the European part of Turkey [11]. In contrast, for German origin inhabitants, the prevalence of 0.4 per 100,000 inhabitants was comparable to that in Great Britain and the USA [11]. The male-to-female ratio was 1.4:1. The average onset age was 27.4-27.7 years (Table 3) in 2012 and 2015 [11, 12]. Table 3 shows the reported

data on average; the first disease manifestation occurs at similar ages in Iran and Germany (average age of first manifestation — Iran: 28.3 years; Germany: 27.7 years) [7, 11]. There was a non-significant difference in the average age of disease manifestation for patients of Turkish and German origin (patients of Turkish origin: 27 years; German origin: 28.8 years) [11]. Furthermore, Table 3 shows that the ratio between male and female patients was also similar in Iran and Germany (Iran: 1.3:1, Germany: 1.4:1) [7, 11]. This statement only applies to the overall German study population. Among the subgroup of German patients, ABD was more common among women than men. In the subgroup of Turkish and Iranian patients, ABD was observed more among men than women.

**Table 3:** Age of onset manifestation and gender distribution in Iran and Germany

Country	Average age of manifestation	Male: Female
Iran (2005)	26.0	1.19:1
Iran (2010)	26.0	1.22:1
Iran (2016)	28.3*	1.3:1
Germany/ Berlin (1994)	25.0	2.26: 1
Germany (1997)	24.5	1:1
Germany (2012)	27.7	1.4:1
Patients of German origin in Germany	28.8	0.9:1
Patients of Turkish origin in Germany	27.0	1.9:1
Germany (2015)	27.4	1.39:1

\* This is because only the adults (>16 years) were included in the study.

**Initial clinical manifestations in ABD patients**

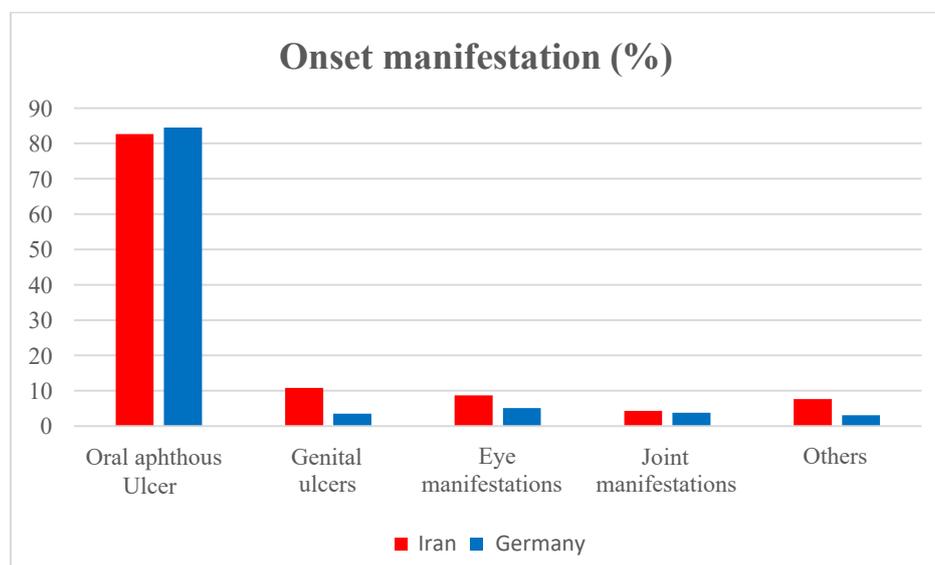
ABD is manifested between 20 and 40 years of age in both countries. The onset symptoms described in Iran in 2016 included recurrent oral aphthous ulcers (82.7%); recurrent genital aphthous ulcers (10.8%; 12.9% in female and 9.1% in male;  $P < 0.0001$ ); eye manifestations such as retinal vasculitis (0.4%; 0.2% in female and 0.5% in male, ns) and uveitis (8.3%; 8.5% in female 8.5% and 8.2% in male; ns); joint inflammation (4.3%; 4.1% in female and 4.5% in male 4.5%; ns) and other lesions (7.7%;

6.0% in female and 9.0% in male;  $P < 0.0001$ ) [7]. In 2012, recurrent oral aphthous ulcer were the onset manifestation in German patients (84.5%), followed by ocular manifestations in 5.1%, joint manifestations in 3.8%, and recurrent genital aphthous ulcers in 3.5%, and others (erythema nodosum in 1.6%, folliculitis in 0.9%, superficial thrombophlebitis 0.6%) in 3.1% [11].

Table 4 and Figure 1 compare the onset manifestations extracted from the Iranian study results in 2016 with the German study results from 2012.

**Table 4:** Onset manifestations in Iranian (2016) and German (2012) patients (%)

Symptoms	Iran	Germany
Oral aphthae	82.7	84.5
Genital aphthous ulcers	10.8	3.5
Eye manifestations	8.7	5.1
Joint manifestations	4.3	3.8
Other	7.7	3.1



**Figure 1:** Comparison of ABD onset manifestations in Iran and Germany

**Major manifestations**

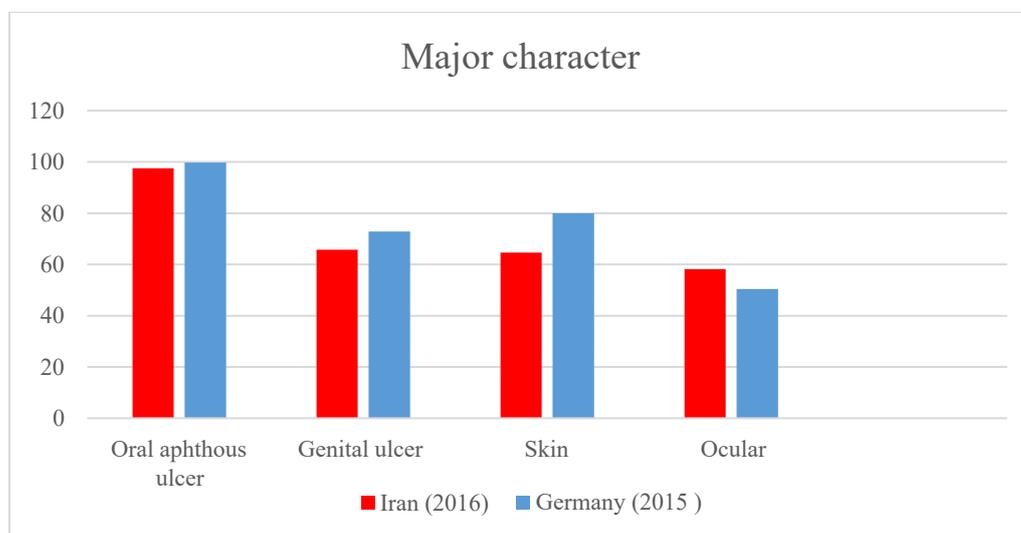
The Iranian study from 2016 showed significant differences in the major signs between male and female patients. There were significantly more recurrent genital aphthous ulcers among women (Iran 65.7%, 68.9% female, 63.2% male;  $P < 0.0001$ ). Dermatological manifestations (Iran 64.6%, 57.1% female, 70.5% male;  $P < 0.0001$ ) and ocular lesions (Iran 58.1%, 51.7% female, 63.0% male;  $P < 0.0001$ ) were observed significantly more among the male patients [7]. There was no statistically significant difference regarding recurrent oral aphthous ulcer between both sexes (Iran 97.5%, 97.0% female, 97.8% male) [7]. The German study from 2015 reported that regarding major signs, more

female patients suffered from recurrent genital aphthous ulcers than male patients (Germany 72.8%, 83.8% female, 65.2% male;  $P < 0.0001$ ). In contrast, dermatological manifestations (Germany 79.9%, 74.0% female, 84.2% male;  $P < 0.001$ ) and ocular lesions (Germany 50.4%, 43.2% female, 55.3% male;  $P < 0.002$ ) were most commonly observed among male patients [12]. No significant difference was detected for recurrent oral aphthae between the two sexes (Germany 99.7%, 99.7% female, 99.8% male) [12]. The distribution of the major signs between the two sexes of the German study results corresponds to those of the Iranian study results. [Table 5](#) and [Figure 2](#) compare the major signs of the Iranian study results from 2010 and 2016 with the German study results from 2012 and 2015. It can be observed that genital

**Table 5:** Comparison of major clinical characters Iranian and German patients (%)

Major Characters								
Country	Year	n	OA (%)	GA (%)	Skin (%)	Eyes (%)	M:F	Onset age (years)
Iran	2010	6500	97.3	64.6	64.9	56.8	1.22:1	26
	2016	6075	97.5	65.7	64.6	58.1	1.3:1	28.3
Germany	2012	721	98.5	64.7	73.4	51.6	1.4:1	27.7
	2015	747	99.7	72.8	79.9	50.4	1.39:1	27.4

OA, oral aphthous ulcer; GA, genital aphthous ulcers; Skin, skin manifestations; Eyes, ocular manifestations (uveitis, retinal vasculitis); M:F = male-to-female ratio



**Figure 2:** Comparison of major clinical signs between patients from Iran and Germany

ulcers, oral aphthae, and skin manifestations were more common among the German cohort than in the Iranian cohort, irrespective of gender. On the other hand, ocular lesions had a higher frequency among Iranian patients than among German patients [7,12], whereas the differences – except for skin lesions – were rather minor.

**Minor manifestations**

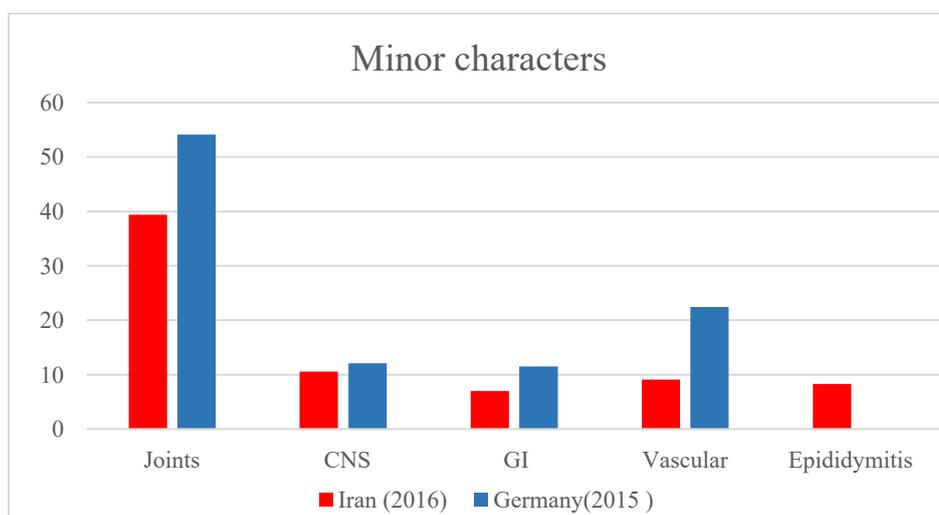
Minor signs, including joint manifestations (Germany 54.1%, Iran 39.4%), neurological manifestations (Germany 12.1%, Iran 10.6%), gastrointestinal manifestations (Germany 11.5%, Iran 7.0%), and vascular manifestations (Germany 22.4%, Iran 9.1%) were more frequent among the German cohort [7, 12].

German study from 1997 showed that epididymitis had an incidence of 15.9% [1]. In 2010, an international study from Iran reported that epididymitis frequency was 8.8% in Germany and 5.6% in Iran [21]. In another German study in 2012, epididymitis was reported in 10.8% of the overall study population. In comparison, prostatitis/epididymitis was twice as common in patients of German origin (15.3%) than in patients of Turkish origin (7.4%) [11]. An Iranian study from 2016 shows that epididymitis frequency was lowest among Iranian patients (4.6%) [7]. [Table 6](#) compares Iranian studies from 2010 and 2016 with German results from 2012 and 2015. [Figure 3](#) compares the minor signs in the 2016 Iranian and 2015 German studies. The German study from 2015 contained no

**Table 6:** Comparison of minor clinical signs in Iran and Germany (%) [4, 7]

Country	Year	N	Minor Characters				
			Joints (%)	CNS (%)	GI (%)	Vascular (%)	Epid (%)
Iran	2010	6500	37.4	3.7	7.4	8.3	4.7
	2016	6075	39.4	10.6	7.0	9.1	4.6
Germany	2012	721	52.4	11.7	12.6	21.2	10.8
	2015	747	54.1	12.1	11.5	22.4	*

\* data not available. Joints, joint involvement; CNS, central nervous system, GI, gastrointestinal involvement; Vascular, vascular manifestations; Epid, epididymitis,



**Figure 3.** Comparison of minor clinical signs between Iran and Germany

information on epididymitis. Recurrent oral aphthous ulcer were found in a German study from 1995 in over 80% of patients on the tongue (80%), lips (79%), and buccal mucosa (74%), with involvement in almost two-thirds of the

gingiva (60%) and less than one-third on the tonsils (30%), palate (28%), and pharynx (25%) [22] (Table 7). The study results from 2016 show that 97.5% of Iranian patients suffer from oral aphthous ulcer [7].

**Table 7:** Localization frequency of oral aphthae in Germany

Localization	Frequency (%)
Tongue	80
Lips	79
Buccal mucosa	74
Gingiva	60
Tonsils	30
Palate	28
Pharynx	25

Recurrent genital aphthous ulcerations can range from millimeters to centimeters in size and heal after ten days to 4 weeks with or without scarring. They usually occur simultaneously with – but less often than - oral aphthae. In men, two-thirds of aphthae were located on the scrotum and penis, and in women, more than 80% were

on the vulva, with almost half of the cases on the vaginal mucosa (Table 8) [22]. Table 8 displays the study results from Germany from 1995 that compare the frequency and localization of genital aphthous ulcers among the two sexes. This study from Germany also showed that genital aphthae are more common in

**Table 8:** Localization of genital aphthous ulcers

Women		Men	
Localization	Frequency (%)	Localization	Frequency (%)
Vulva	82	Scrotum	69
Vaginal mucosa	46	Penis	67
Inguinal	10	Inguinal	15
Cervix	8		

women in the vulva area than in the cervix. They are also more common in men in the scrotum and penis than in the inguinal area. Furthermore, 2016 study results showed that 97.5% of Iranian patients suffer from oral aphthae. Moreover, in a study from 2016 from Iran, 70.5% of male and 57.1% of female patients suffered from skin lesions. In a study from 2015 from Germany, 84.2% of male and

74% of female patients suffered from skin lesions [7,12]. Table 9 compares the results of an Iranian study from 2016 with those of a German study from 2012 regarding the different skin lesions and their frequencies [7,11]. Table 9 shows that skin lesions occur more frequently in Germans than in Iranian subjects. The Iranian study provided no data regarding superficial thrombophlebitis and pyoderma [7, 11].

**Table 9:** Skin manifestations in comparison between Iranian and German patients

Manifestation	Iran (%)	Germany (%)
Pseudofolliculitis	53.2	58.7
Erythema nodosum	23.9	37.4
Other (ulcerations)	7.4	10.9
Superficial thrombophlebitis	2,3	11.3
Pyoderma	*	11.9

\* = No data could be determined from Iran in 2016

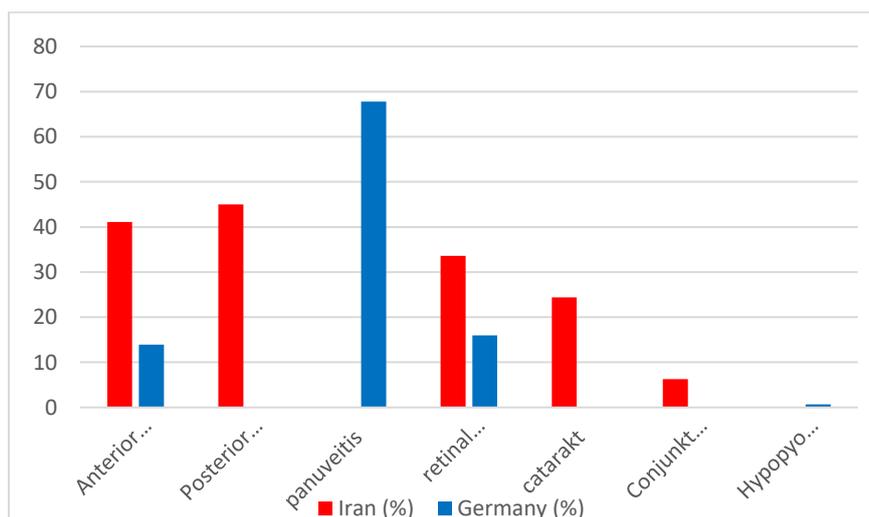
[Table 10](#) [7,11] and [Figure 4](#) compare ocular manifestations reported in international studies from Iran and Germany. Compared with Germany, anterior uveitis was more common in Iran (Germany 13.9%; Iran 41.1%) [7, 11]. The frequency of panuveitis in Germany is 67.8%. The classic ocular lesion in ABD, panophthalmitis involving all these three parts, was seen in 21.2% (CI: 1.1) of Iranian patients. Panuveitis was present in 12% (CI: 0.9). Therefore, the total frequency of panuveitis would be 33.2% in Iranian patients [31].

Retinal vasculitis occurs twice as often in Iranian patients (33.6%) as in German patients (16%). In Iranian ABD patients, cataracts were reported at 24.4% and conjunctivitis at 6.3%. No studies are available regarding the frequency of cataracts and conjunctivitis in German ABD patients since these clinical signs are not considered associated with ABD. The frequency of papillitis among German ABD patients was reported to be 0.7%, while no studies were found regarding the frequency of papillitis among Iranian ABD patients.

**Table 10:** Ocular manifestations in comparison between Iranian and German patients

Symptoms	Iran (%)	Germany (%)
Uveitis anterior	41.1	13.9
Posterior uveitis	45	*
Panuveitis	33.2	67.8
Retinal vasculitis	33.6	16
Cataract	24.4	36.8
Conjunctivitis	6.3	*
Hypopyon & Papillitis	*	0.7

no more recent data could be determined from Germany in 2012 and Iran in 2016



**Figure 4:** Frequency distribution of ocular manifestations in Iran and Germany

## Discussion

This work compared the demographic data and clinical manifestations of ABD in Iran and Germany. Epidemiological studies have confirmed that geographical as well as environmental factors might contribute to the development of this disease [3]. Although these two factors play a major role, possible agents,

e.g., viruses and bacteria, as further triggers of the disease should not be neglected [3]. Countries that are located along the Silk Road show a higher ABD prevalence than the rest of the world [5]. Interestingly and despite the different origin of patients in these two countries we could detect similar distribution in the majority of extracted data with the exception of the disease

prevalence. Reported prevalence in other countries comes from Japan with 13.5–30.5 patients per 100,000 inhabitants, Korea with 7.3–30.2, Iraq with 17 [25, 26], United States with 8.6 [7, 21], France with 7.2 [7, 21], Germany with 0.9–4.2/100,000 [11, 12], Portugal with 1.53 [27], Northern European countries with 1.18 [26–28] and UK with 0.64 patients per 100,000 inhabitants [26–28]. Thus, in Turkey, Israel, China, Iran, Japan, Korea and Iraq the prevalence of ABD is much higher than in Western European countries. In the countries compared in this study, namely Iran and Germany, a significant difference in prevalence, 80 versus 0.9 ABD patients per 100,000 inhabitants, respectively, was shown [7,11]. However, the gender distribution was similar with a male-to-female ratio of 1.3:1 in the most recent study from Iran (2016) [7] compared with 1.4:1 in Germany (2012) [11]. The average age of manifestation in the 2016 study from Iran was 28.3 years [7], which is also comparable to the average age in Germany of 27.4 years [12] and the global average of 28.1 years [29]. The first clinical manifestation is predominantly found between 20 and 40 years of age with comparable occurrence of oral aphthae (82.7% in Iran, 84.5% in Germany) [7,11] as an onset sign. The occurrence of major clinical signs was also similar in the two countries. A limitation of this study concerns the data of the ABD patients registries and do not reflect the data of all patients with the disease.

### Conclusions

Our study indicates no influence of the genetic and/or environmental background on the epidemiology and clinical manifestation of ABD at least among patients in Iran and Germany, despite the significant difference in the prevalence of the disease. The current data together with the fact that the prevalence of the disease in Turkish origin patients living in the European part of Turkey and Germany is equal, at least dispute older data reporting differences in the prevalence of the disease associated with environmental factors

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### Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this study.

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