Review Article

Prevalence and Clinical Investigation of the Behcet's Disease in Middle East and North Africa: A Systematic Review and Meta-Analysis

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Abstract

Context: This systematic review and meta-analysis was performed to determine the prevalence (by overall relative frequency) and clinical information of the Behcet's disease in Middle East and north Africa (MENA) and it has an important effect on the health policy and performing complementary studies in future.

Evidence Acquisition: We performed this systematic literature review from several databases including PubMed, Scopus and ISI Web of Science according to search strategy with two filters, place (MENA countries) and time (all articles published from Jan 1980 to Jan 2016 were considered). The keywords such as "Behcet's syndrome", "Behcet's disease", "triple symptom complex", "Middle East" were searched. Out of 4013 relevant articles and according to inclusion and exclusion criteria, 28 papers were selected to study. To examine the quality of the studies, all papers were evaluated independently by two authors and the Kappa coefficient was 95%. Afterwards, the critical appraisal was performed by strengthening the reporting of observational studies in epidemiology (STROBE) form. Due to sever heterogeneity, the pooled prevalence (per 100,000 people) was derived by the random effect model that takes between-study variation into account.

Results: According to the results of the present study, the prevalence rate of BD in Iran was 68; it was after Turkey among MENA. The pooled prevalence (per 100,000 people) of BD in MENA was 120 (95% CI: 86.8, 166.8) according to the random effect model. The oral aphthosis was the most frequent symptom among other symptoms and HLA-51 association was its poor prognosis. Turkey had the highest prevalence (per 100,000 people) of 420 (95%CI: 340, 510) and the lowest prevalence 2.1 related to Kuwait in MENA countries.

Conclusions: There are different statistics about the prevalence rates of the disease that have been published; these different prevalence statistics can be explained by racial and geographical divergence, patient selection and BD diagnosis criteria. The results of this study can be useful for health policy and other studies which are needed to find the reasons of this prevalence difference.

Keywords: Behcet's Syndrome, Behcet's Disease, Triple Symptom Complex, Middle East

1. Context

Behcet's disease (BD) is a systemic complex disorder characterized by recurrent attacks of inflammation (1). It is an inflammatory disorder of unknown cause and the most important clinical manifestations are mucocutaneous and ocular signs and symptoms (2). Major symptoms of the Behcet's disease are oral aphthos, uveitis, skin lesions, and genital ulcerations. Involvement of the gastrointestinal tract and vessels is less frequent but has poor prognostic symptoms (3); it is probably associated with HLAB51 allele (4). Environmental factors such as bacterial and viral factors have also been involved in its pathogenesis (5). Behcet's disease was seen in the silk road countries, but due to some reasons such as immigrations, it is now seen throughout the world (6). Its geographical distribution is from japan to Mediterranean sea (1). Its prevalence is not high in northern Europe and United States. Despite the priority of the problem, there is an obvious gap in required knowledge evidence-based planning of relevant policies. The aim of our review was to investigate the prevalence of BD, and compare its clinical manifestations in Middle East and north Africa.

1.1. Objectives

Considering the importance of the effect of epidemiology studies on better management and control of BD, especially for health policies, this review aimed to investigate the prevalence of BD and compare its clinical manifestation in Middle East and north Africa.

2. Evidence Acquisition

2.1. Search Strategy

We searched three databases containing PubMed, Scopus and ISI Web of Science from Jan 1980 to Jan 2016. The search was performed on the titles, abstracts, or keywords of each article using keywords and phrases separated by the Boolean operators ("Behcet syndrome" or "Behcet disease" or "triple symptom complex") and ("Middle East" or "the name of countries of MENA") and (Filters: Publication date from 1980/01/01 to 2015/12/31; Humans) and (Filters: Non-English language). For each paper that had not presented clear data or complete data, we sent at least three Emails to the corresponding author. The reference lists of all retrieved articles were searched manually at the same time. Hand searching was done too. Also, strengthening the reporting of observational studies in epidemiology (STROBE) form for quality assessment was utilized. Meta-analysis was performed to determine the prevalence and clinical information of the Behcet's disease in Middle East and north Africa (MENA).

2.2. Study Selection

According to the inclusion criteria, 4013 articles were selected; 3784 articles were excluded due to irrelevant topic and 229 remained, in the second step, 78 duplicate articles were removed and 151 remained. Two articles were excluded due to non-English language. Three papers were excluded in the critical appraisal step by the STROBE form, 124 articles were removed due to nonrelated topic, and six papers were added in hand searching. Finally, according to the exclusion criteria 28 papers remained to study (Figure 1).

2.3. Inclusion Criteria

We included all studies on the Behcet's disease including local, and subnational studies and national surveys, which were conducted in Middle East and north Africa countries. We excluded nonrelated articles, those with duplicate citation, non-English or low qualified in STROBE form. (More details have shown in the Figure 1, Table 1).

Table 1. Search Strategy

Search Strategy	Description
	("Behcet syndrome" , "Behcet disease" or "triple symptom complex") and ("Middle East", "Afghanistan", "Bahrain", "Iran", "Iraq", "Israel", "Jordan", "Kuwait", "Lebanon", "Oman", "Qatar", "Saudi Arabia", "Syria", "Turkey", "United Arab Emirates", "Yemen", "Africa, Northern", "Algeria", "Egypt", "Libya", "Morocco", or "Tunisia") and (Filters: Publication date from 1980/01/01 to 2015/12/31; Humans) and (Filters: Non-English language)

2.4. Data Extraction

The extracted data from papers included first author's name, year of publication, study region, total sample size, age and sex groups, clinical findings, reported prevalence and its 95% confidence interval (CI). Data extraction was carried out in duplicate by the first and second authors.

2.5. Quality Assessment

The critical appraisal was performed by STROBE form, we scored topic critical appraisal, 0 - 2 and the article score was 8 - 15, less than eight was excluded. All of the costs of quality assessment and data extraction were followed independently by two authors based on title, abstract and keywords. The Kappa coefficient was 95%. Disagreements were resolved by consensus of the whole team in both phases.

2.6. Data Synthesis and Analysis

The numbers of total participants with the Behcet's disease were used to estimate the relative frequency (RF), which then converted to log RF and its standard error (SE) for the meta-analysis (7). The heterogeneity and the variation in pooled estimation were assessed using the Cochran's Q test and I-squared, respectively (7). Due to severe heterogeneity, the pooled prevalence was derived by the random effect model that takes between-study variation into account (8). In order to examine the value which the pooled prevalence might depend on, sensitivity analysis was used for a particular study or a group of publications. Publication bias was checked by Begg's funnel plots and asymmetry tests including the Egger's regression asymmetry test and Begg's adjusted rank correlation test (8) (Figures 2 and 3). All statistical analyses were conducted using the STAT 11.0 (STATA Corp, College Station, TX) and P values under 0.05 were considered statistically significant (Figure 4).

3. Results

The prevalence of BD is high in Turkey, Iran, and Tunisia respectively among countries in MENA. Five studies concerning the epidemiology of BD were conducted in Turkey. They showed the BD prevalence between 19 and 420 (per 100,000 people), two most important studies were conducted by Azizlerli and Necati Ç akır. In the first study, 23,986 people were recruited and 101 (52 males and 49 females) patients were detected. The prevalence in this study was 420 and in the second study 15,280 inhabitants participated; according to the ISG for the Behcet's disease there were 3 patients (two males and one female), with the mean age of 40 and the prevalence rate of 19.
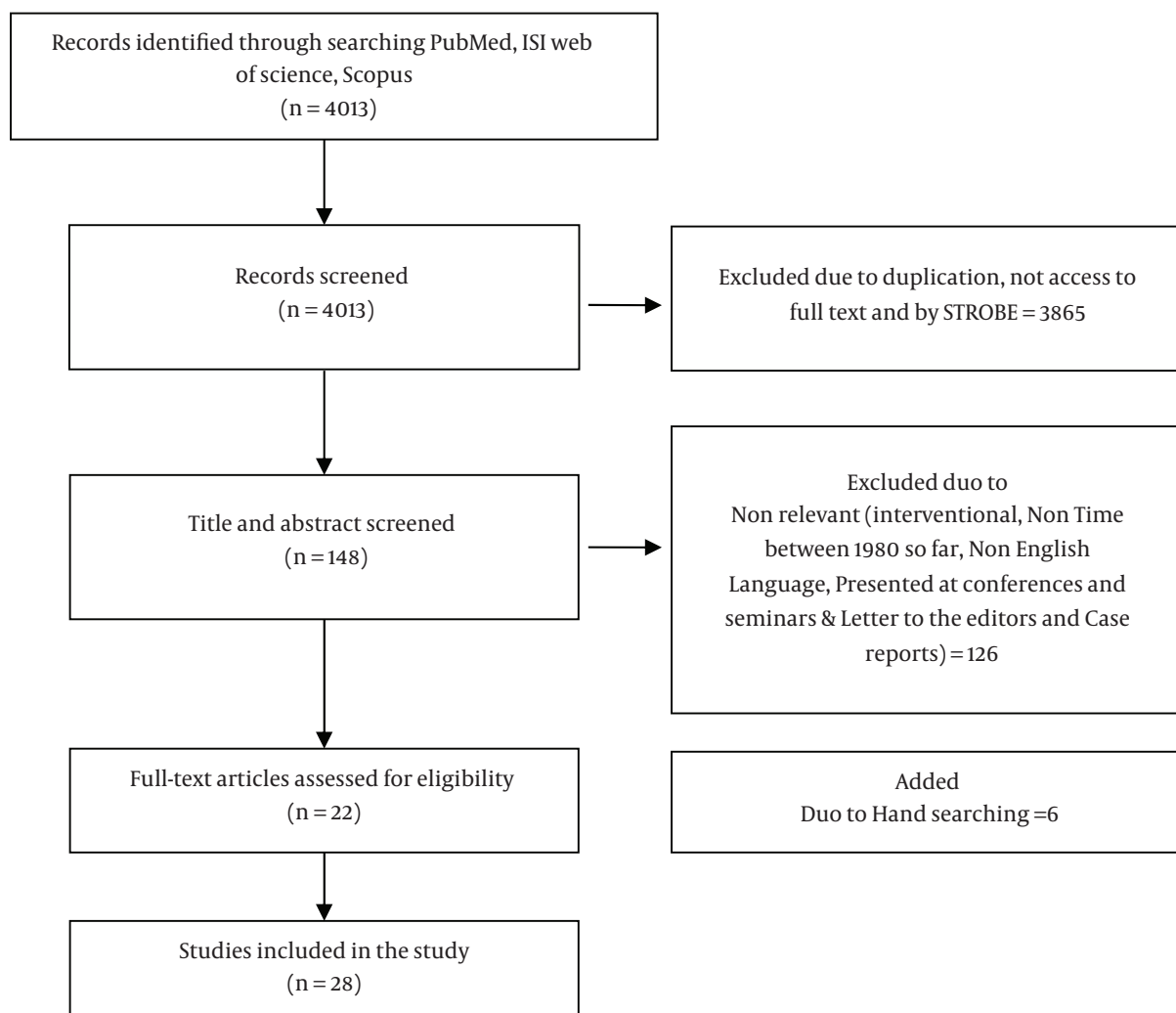
Figure 1. Flow Diagram for Study Selection Progress

The prevalence rate was between 16 and 68 (per 100,000 people) in Iran. Two investigations were performed in 2007 and 2010 by Davatchi et al. Also, 10,291 people were recruited in that study in 2005. There were seven BD patients, three males and 4 females and the prevalence rate was 68 but in the another study (9), the prevalence rate was 16, the female to male ratio was 1:1/4 and mean age was 26.2 ± 9.6. In this study, 6,000 cases were recruited and assessed and one BD diagnosed. Diagnostic criteria was clinical not particular. In Kuwait, a survey was conducted in 1986 by Al Mahdi Mousa. Twenty-nine events occurred (22 males, 7 females) and the prevalence rate was 2.1, it is the lowest rate among MENA. In Saudi Arabia, the BD prevalence rate was 20, mean age was 29.3 and the female to male

ratio was 1:3/4.

We found that the pooled prevalence of BD in MENA was 120 (CI: 86.8, 166.8) according to the random effect model. The results of heterogeneity showed that the prevalence of BD in the study was heterogeneous ($I^2 = 96\%$ P value < 0.001 according to the chi-square test).

3.1. Clinical Information

One of the clinical manifestations that BD is diagnosed by, is mucocutaneous lesions, such as pseudo folliculitis, oral and genital aphthosis, erythema nodosom, and ophthalmological features (8). Iranian data in this area is derived from two important studies that have been conducted by Davatchi et al. in 2003 and 2007. Table 3 shows
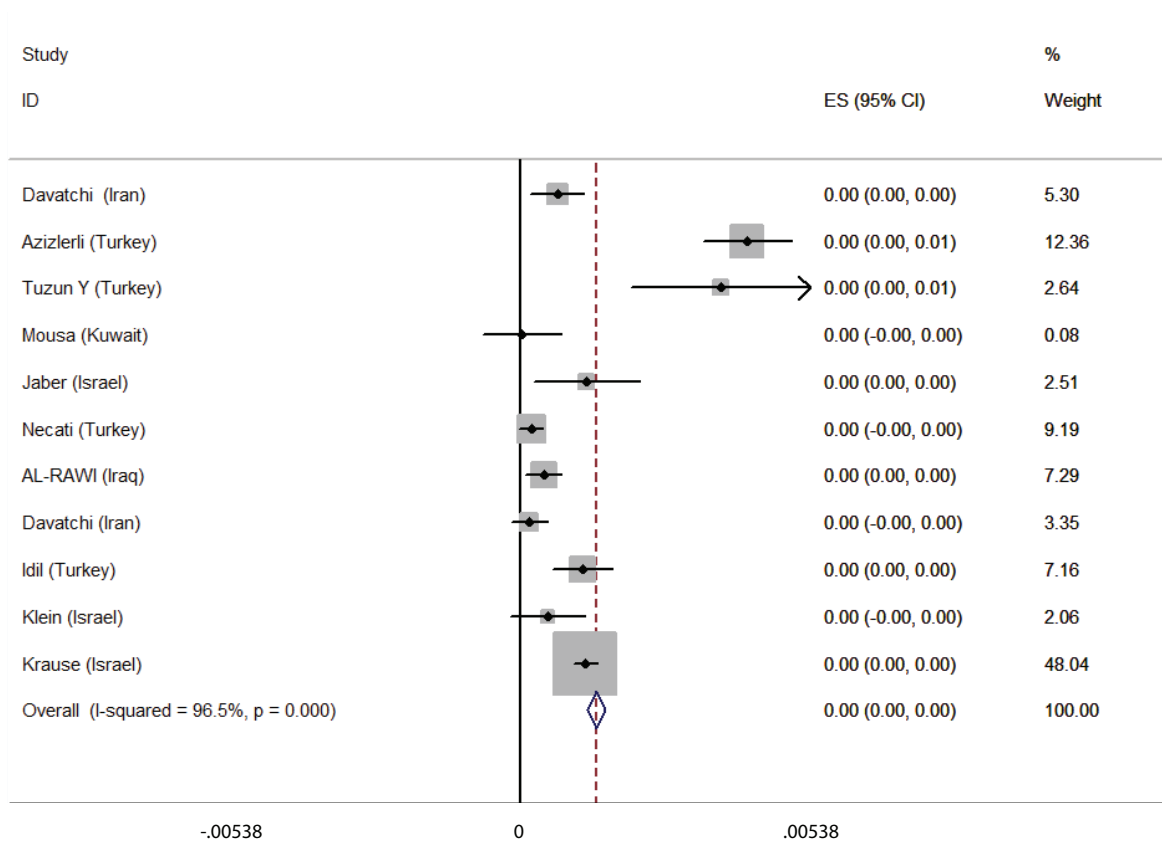
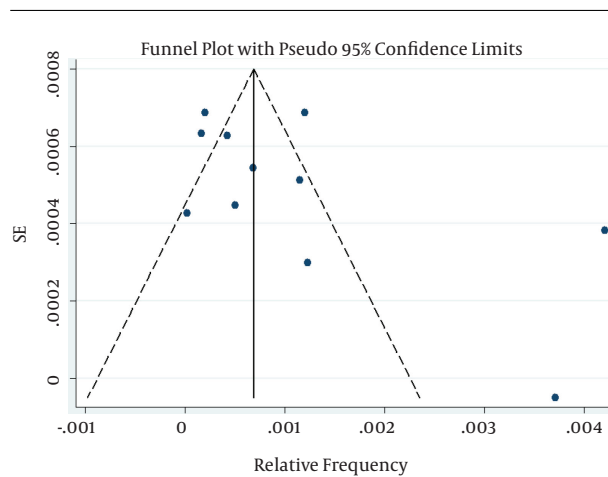**Figure 2.** Forest Plot of the Behcet's Disease Prevalence in MENA

Figure 3. Funnel Plot of the Prevalence of the Behcet's Disease in MENA

this data briefly.

The mean frequency rate of oral aphthosis (OA) in all studies conducted in Turkey was 99.9% $\pm$ 0.17. The mean of oral aphthos in Iran was 97.4% $\pm$ 2.2. In Saudi Arabia, Tunisia and Egypt, the frequency rates of OA were 100%, 98%, and 100%, respectively (Table 3). Oral aphthosis is the most common symptoms of BD (1) and it is usually an initial symptom; other symptoms were pain and lesions with well-defined borders and a necrotic base. Oral ulcers involve gingiva, tongue, buccal and mucosal membranes. It is covered by a yellow membrane (3).

The mean genital aphthosis (GA) frequency in Iran was 76.4% $\pm$ 20.4. Mean genital ulceration in all Turkey studies showed 80.4% $\pm$ 7.3 and in Saudi Arabia, Tunisia and Egypt, were 87%, 79% and 94%, respectively (Table 3). They usually begin like a papules or pustules that ulcerate in a short time. They are mostly painful and have a punched-out shape. They have edematous border and their base is covered with yellow fibrin. They usually appear in males in the scrotum, penis, inguinal area, and pubis. However, in females the genital aphthosis usually appears in vulvae, major and minor labia, the cervix and the vagina (2).
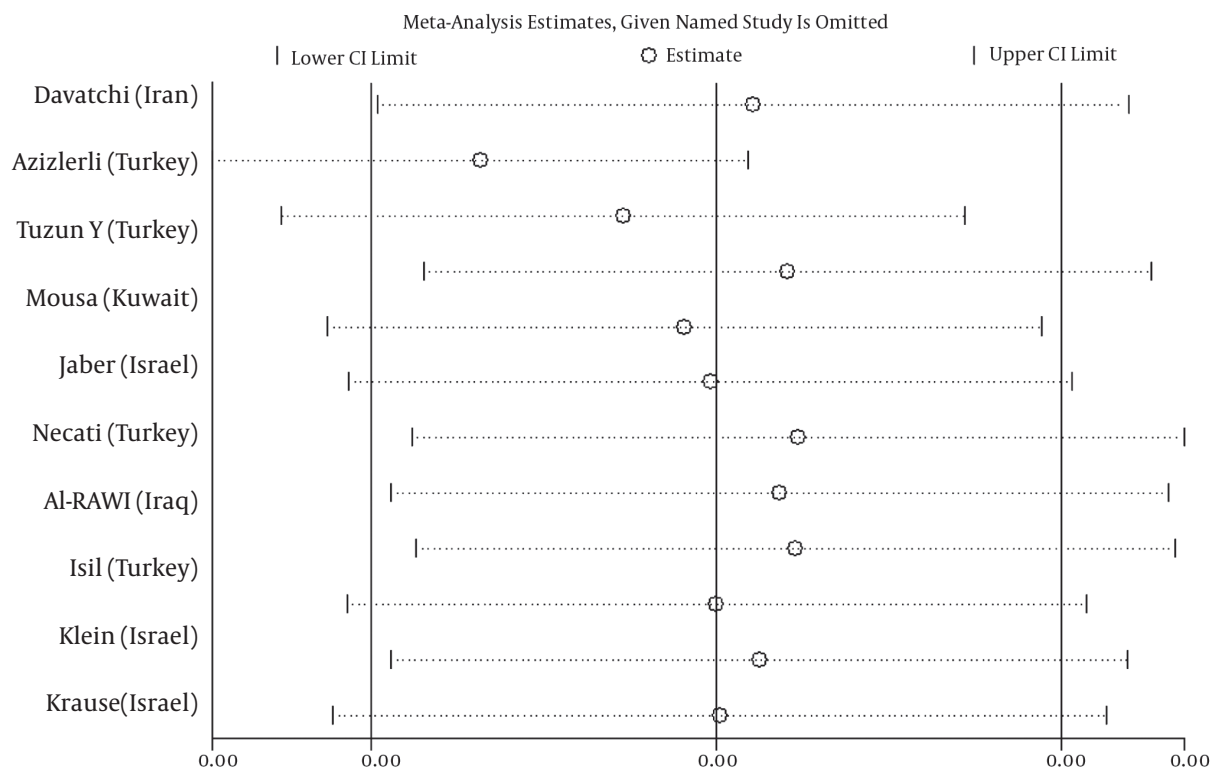
The mean values of ocular lesions were 26.4% $\pm$ 18.7

Figure 4. Sensitivity Plot of the Prevalence of Behcet's Disease in MENA

Table 2. Prevalence Investigation of the Behcet's Disease in Middle East and North Africa During 1980 - 2016

Author	Country	Publish, (year)	Total Number Samples	Number of Patients	Male	Female	Age	Prevalence (95% CI) (per 100,000)
Davatchi F	Iran	2007	10291	7	3	4	15 - 70	68 (30, 150)
Azizlerli	Turkey	2003	23986	101	52	49	14 - 68	420 (340, 510)
Yurdakul S,	Turkey	1988	5131	19	6	13	> 14	370 (230, 590)
A. R. a1 Mahdi Mousa	Kuwait	1986	150	29	22	7	13 -52	2.1 (1.3, 2.6)
Ilan Krause	Israel	2006	93230	112	-	-	33	120 (100, 140)
Jabber	Israel	2002	4876	6	1	5	$\geq$ 10	120 (50, 280)
Necati C¸akır	Turkey	2011	15280	3	2	1	40	19 (10, 60)
Z.S. AL-RAWI	Iraq		14155	6	4	2	33.16 ± 5.7	17 (10, 35)
Al-Dalaan AN,	Saudi Arabia	1994	190	46	-	-	29.3	20 (18, 31)
Davatchi F,	Iran	1997	6000	1	1	-	26.2 ± 9.6	16 (0. 110)
Aysun Idil	Turkey	2002	13,894	16	5	11	10 - 97	110 (70, 200)
Pinchas Klein	Israel	2010	4000	2	1	1	29	50 (10, 200)

in Turkey, 56.9% $\pm$ 0.95 in Iran, 56% in Saudi Arabia, 51% in Tunisia and 41% in Egypt. Anterior uveitis (AU) is an inflammatory painful lesion, photophobia, and loss of vision. When attacks become successive, they produce se-

quel, which lead to cataract, and probably glaucoma. Posterior uveitis (PU) and retinal vacuities (RV) are the most important causes for the visual disturbance (10).

Mean joint involvement was 37.3%±3.6 in the Iranian patients. It was 41.5% ± 17.5 in Turkey, 40.6% ± 10.3 in Iraq, 69% in Kuwait, 55% in Jordan and 65% in Lebanon. Different kinds of musculoskeletal and joint involvement are seen in patients with BD such as arthralgia, sacroilitis, and arthritis (monoarticular, oligoarticular, polyarticular) and they were noted mostly in knees, ankles and wrists (11). Joint manifestations are not erosive, lasting several weeks to several months.

Most neurologic manifestations are seen from cognitive behavioral problems to organic disorder, as well as seizures, headache, benign intracranial hypertension, diencephalon dysfunction, pseudo bulbar palsy, brainstem syndromes, cranial nerve palsies, hemiplegia, cerebellar syndromes, and myelopathy (10). Neurological manifestations were 44% in Saudi Arabia, 14.2% in Egypt, 14% in Kuwait, 5% in Jordan, 14% in Lebanon and 16.6% in Iraq. It was 3.3% in Iran. The other manifestations have been showed in Table 3.

4. Conclusions

The Behcet disease is a multisystem inflammatory disorder (10) with unknown etiology and lacking any specific therapy (21). The most important clinical symptom in BD is oral aphthosis in nationwide surveys and its frequencies are close together in MENA countries. Genital aphthosis has the second most frequency. Five studies have been conducted in turkey, three in Iran, three in Iraq, two in Saudi Arabia, two in Tunisia, two in Egypt, three in Israel, one in Kuwait, one in Morocco, one in Algeria, two in Jordan and one study in Lebanon. The highest prevalence was related to Turkey and the lowest related to Kuwait. They reported different statistics, and the differences in manifestations was explained by racial, and geographical divergence, patient selection and BD diagnosis criteria. The Behcet's disease is not rare in Iran; the annual incidence rate is around 280 patients (23). Therefore, comparison of our data with other reports may be interesting (Table 2). Our data show more similarity with those of Turkey. The prevalence of BD in Iran (68) is near the one calculated in Turkey (80). Turkey has the highest prevalence (19 - 420) and the lowest prevalence (2.1) is related to Kuwait in MENA countries. It was highly heterogeneous. We found that the pooled prevalence of BD in MENA was 120 (CI: 86.8, 166.8) according to the random effect model ($I\hat{}2 = 100\%$, P value < 0.001 according to the chi-square test). The prevalence rate in Iran is 68% and it is after Turkey among MENA. Oral aphthosis is the most frequent symptom among other symptoms and

HLA-51 association makes it poor prognosis; considering the previous studies, this study has several achievements. This study presents scientific evidences to depict the Behcet's disease in Middle East and north Africa. All available sources of data were searched using standard protocol. According to our knowledge, this is the first systematic review of the Behcet's disease in Middle East and north Africa that provide practical information on the Behcet's disease prevalence and its clinical manifestations. The results could be useful for policy-making in health system and designing more surveys in this field. This systematic review can be useful for the future complementary study. There are different statistics about prevalence and clinical features, that has been published and it is explained by racial, and geographical divergence, patient selection and BD diagnosis criteria. Based on our best of knowledge it is the first comprehensive study on the Behcet's disease in Middle East and north Africa.

The present study has some limitations. The validity and applicability of our systematic review depends on the quality of the primary studies that are included. Heterogeneity of searched results limits the generalization of our findings. We had also some limitations in availability of some complementary data that were following through corresponding authors of the papers (30).

Footnote

Authors' Contribution: Mohammadtaghi Palizgir contributed to concept and design of the study and manuscript preparation; Mahdi Mahmoudi contributed to manuscript preparation; Mostafa Qorbani contributed to data collection and analysis; Shirin Djalalinia helped in performing search strategy; Shayan Mostafaei helped in data analysis and meta-analysis and Farhad Shahram contributed to concept and design of the study and manuscript preparation.

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Table 3. Summarized Clinical information of Behcet's disease in Middle East and north Africa[a]

Country	Case No	OA	GA	Skin	Eye	Pathergy	CNS	PID	Pulmonary	Phl	Arthritis	EN
Iran (2)	16	100	75	50	43.7	5.9	-	-	-	-	-	-
Turkey (12)	2147	100	88	54.2	28.9	22	0	1	10.6	15.9	47.6	28
Turkey (13)	3443	95.8	64	65.8	57.8	3.3	6	0.7	6.3	39.9	22.9	-
Turkey (14)	496	99.6	76.7	77.8	Not	7.7	Not	18.2	38	46.9	-	4.9
Tunisia (15)	716	98	79	62	51	31	2	1.4	23	35	-	4
Saudi Arabia (16)	145	100	87	57	56	44	4	14	25	37	-	4
Iraq (17)	60	97	83	48	33	2	22	Not	17	48	55	10
Egypt (18)	34	100	94	29.4	41	14.7	Not	0	5.9	61.7	20.5	0
Israel (19)	69	100	40	74	30	28	0	0	23	8	Not	26
Kuwait (20)	29	100	93	76	69	14	Not	34	Not	69	45	21
Jordan (21)	20	100	65	5	65	5	5	5	20	55	5	5
Lebanon (22)	100	99	78	53	63	14	2	4	11	65	25.5	10
Turkey (23)	19	100	73.7	94.7	0	-	-	-	-	47.4	42.1	-
Israel (24)	112	23.7	67.9	36.8	52.70	11.6	-	-	8	69.6	26.3	-
Turkey (25)	9	100	88.9	66.6	33.3	-	-	-	22.2	55.5	44.4	-
Israel (26)	6	100	100	66.7	66.7	16.6	-	0	-	100	-	0
Iran (10)	6500	97	65	65	57	3.8	47	-	6	37	-	7.4
Iran (1)	6	100	83.3	50	40	16.6	-	-	-	33.3	-	16.6
Iran (9)	4704	96.6	65.3	70.3	55.9	3	10.5	-	6.2	34.8	22.3	7.9
Morocco (27)	1034	100	86	-	65	17	-	-	16	52	-	-
Algeria (11)	58	100	70	93	31	14	5.2	-	31	12	-	6.9
Tunisia (15)	519	100	87.5	68	32	12	-	-	25	55	-	-
Jordan (21)	200	100	86.5	90.5	42	38.5	27	-	24	47	-	17
Iraq (28)	330	100	83	-	42	-	-	-	-	-	-	-
Egypt (29)	274	92	76	39	76	26	-	-	-	50.00	-	10
Saudi Arabia (18)	119	100	87	57	65	44	4	-	25	37.00		4

Abbreviations: CNS, central nervous system; EN, Erythema nodosom; GA, genital aphthosis; Phl, phlebitis; OA, oral aphthosis; PID, epididymitis.
[a] Values are expressed as %.

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