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ORIGINAL ARTICLE

Epidemiological and Clinical Features of People with Malta Fever in Iran: A Systematic Review and Meta-Analysis

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Abstract
Objectives: Numerous studies have reported the epidemiological and clinical features of Malta fever incidence in Iran. Review and synthesis of the related literature through meta-analysis can provide an appropriate measurement for aforementioned indices. Therefore, the present study aimed to determine the epidemiological and clinical features of people with Malta fever in Iran.
Methods: The required documents were obtained through searching national and international databases. In each study, standard deviation of the indices was calculated using binomial distribution formulas. Finally, the heterogeneity index was determined between studies using Cochran (Q) and I^2 tests.
Results: Combining the results of 47 articles in the meta-analysis indicated that 57.6% (55.02–60.1%) and 42.3% (49.8–44.9%) of the patients were male and female, respectively. Most of the patients lived in rural areas; 68.4% (63.6–73.2%) compared to 31.4% (26.7–36.3%). In addition, 20.8% (17.4–24.2%) of the patients were ranchers and farmers, 16.9% (14.5–19.4%) were students, and 31.6% (27–36.2%) were housewives. Of the patients studies, 50.5% (35.6–65.2%) experienced contact with animals and 57.1% (46.4–67.9%) used unpasteurized dairy products. Fever, joint pain, and sweating were detected among 65.7% (53.7–77.8%) and 55.3% (44.4–66.2%), respectively.
Conclusion: The present study revealed that the frequency of male patients with brucellosis was considerably more than that of female patients. The number of patients with Malta fever in rural areas was significantly more than in urban areas. High-risk behavior, unprotected contact with animals, and using unpasteurized dairy products were among the most significant factors affecting Malta fever incidence in Iran. Fever, joint pain, and sweating were detected among most of the patients with Malta fever.

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1. Introduction

Brucellosis or Malta fever is a bacterial infection that spreads from animals to humans. Despite the preventive measurements adopted throughout the world; particularly in the Mediterranean and Iran; the disease is still a thread to public health [1,2]. Iran stands in the second rank regarding the prevalence of Malta fever worldwide [3]. Malta fever is caused by *Brucella* bacteria, particularly by *Brucella melitensis*, *Brucella abortus*, and *Brucella suis* species. In advanced countries, men are more affected compared with women. Children are more affected than adults. In Iran and other areas, in which brucellosis is endemic, there is no significant difference between infection among children and adolescents. Moreover, since Iranian rural women cooperate with men in farming and animal husbandry, they are also highly susceptible to the disease [4].

The clinical manifestations of people with brucellosis include long-term fever, anorexia, fatigue, or involvement of local organs such as arthritis [5]. Malta fever is transmitted to humans through direct contact with animals or through ingestion of infected dairy products. Therefore, it is considered as an occupational hazard for people involved in cattle-related jobs (e.g., veterinarians, slaughterhouse workers, ranchers, and farmers) [2]. Different factors play a significant role in brucellosis infection in humans. Direct and indirect contact including using unpasteurized dairy products, animal husbandry, and giving birth to ewes are significantly correlated with the disease. Because of its long-lasting effects, Malta fever is known as the disease of a thousand faces [6]. Therefore, identifying and controlling it play a crucial role in improving public health [7]. Moreover, the wide spectrum of brucellosis symptoms in human has led to the fact that diagnosed people are considerably less than the actual number of the infected population [8,9].

A database review indicates that numerous studies are carried out on the epidemiological features of Malta fever in Iran. An authentic measurement for the epidemiological and clinical features of Malta fever can be developed through combination of the research findings using meta-analysis [10]. Furthermore, through systematic review and meta-analysis of the results, we can provide well-grounded findings that can be used in public health policy-making and proposing suggestions for further research. The current research aimed to study the epidemiological and clinical features, and high-risk behaviors of people with Malta fever in Iran through carrying out a meta-analysis.

2. Materials and methods

2.1. Search strategy

Articles published in national and international journals, which were indexed in National Database, SID, Medlib, Magiran, Iranmedex, Scopus International Database, Science Direct, PubMed, and Google Scholar, were searched for relevant articles up to April 14, 2015. The search was looking for Persian and English keywords and the possible combination of important and sensitive terms. The keywords included Malta Fever, Iran, human brucellosis, brucellosis frequency, prevalence, epidemiology, along with using “AND” and “OR” operators in article subjects and abstracts. The Persian equivalents of the words were also searched among published articles. Some Persian databases were not sensitive to the operators, therefore, just Malta fever or brucellosis were searched. To prevent missing any studies and to increase the sensitivity, the references of the papers were also checked. The search was evaluated and reviewed randomly by two other researchers and the results indicated that no article was missed. Furthermore, paper databases were also searched for those articles that were not published electronically. Experts in this field were also consulted to find other unpublished works.

2.2. Study selection

Full text or abstracts, documents, and reports found in advanced searches were extracted. After excluding duplicates, irrelevant articles were also excluded through assessing titles, abstracts, and full texts, and finally the relevant studies were selected. To avoid publication bias (transverse and longitudinal), the studies were assessed and duplicate papers were excluded.

2.3. Quality assessment

The quality of the relevant articles was evaluated using the STROBE checklist (Strengthening the Reporting of Observational Studies in Epidemiology) [11] and another checklist used in a literature review [12]. Items related to study type, sample size, research objectives, population, inclusion and exclusion criteria for primary research, analysis method, and appropriate presentation of results were determined and a score was assigned to each item. Those studies scoring ≥ 8 were included in the research.

2.4. Data extraction

In each primary study, data were extracted based on title, first author name, publication year, sample size, the province in which the study was conducted, research type, residency status, average age, occupation (rancher and farmer, students, housewives), cattle contact history, unpasteurized dairy product usage, and the most common clinical signs (fever, joint pain, and sweating). Data were extracted by two researchers. We then examined the level of agreement between the results obtained by these two researchers.

2.5. Inclusion criteria

Persian and English studies with adequate sample size on epidemiological and clinical features and high-

risk behaviors of patients with Malta fever were selected through the assessment procedure and scoring criteria.

2.6. Exclusion criteria

Studies that did not report the epidemiological and clinical features of Malta fever, those with unknown sample size, abstracts published in conference proceedings that did not include full text, and studies published before 1990 were not included. Case reports, case−control studies, and studies that did not score the minimum in quality assessment, were also excluded.

2.7. Statistical analysis

Stata version 11 (Stata version 11 Corporation, College Station, TX, USA) software was used to analyze the data. The standard error for frequency of epidemiological features, high-risk behavior and, clinical signs of people with Malta fever in each study was estimated using binomial distribution formula. Finally, heterogeneity index between the studies was determined using Cochran (Q) and I^2 tests. Since the study incorporated sources of heterogeneity, a random-effect model was used to calculate the frequency of the epidemiological features, high-risk behavior, and clinical signs of people with Malta fever in Iran. Point estimation of the frequency percentage of epidemiological features, high-risk behavior, and clinical signs of people with Malta fever in Iran were calculated in accumulation graph (forest plots) with 95% confidence intervals.

3. Results

A total of 4,247 articles were found through our primary search in different databases, of which, 3,410 were excluded after narrowing the search results. Afterwards, the titles and abstracts of 837 primary studies were checked, of which, 442 relevant articles remained and 325 articles were excluded due to overlapping of databases. Finally, 117 articles were selected. The references were checked and four articles were found. Four articles were found to be duplicated and were published under two titles in different journals [4,13−19]. After assessing the full text of articles and excluding the

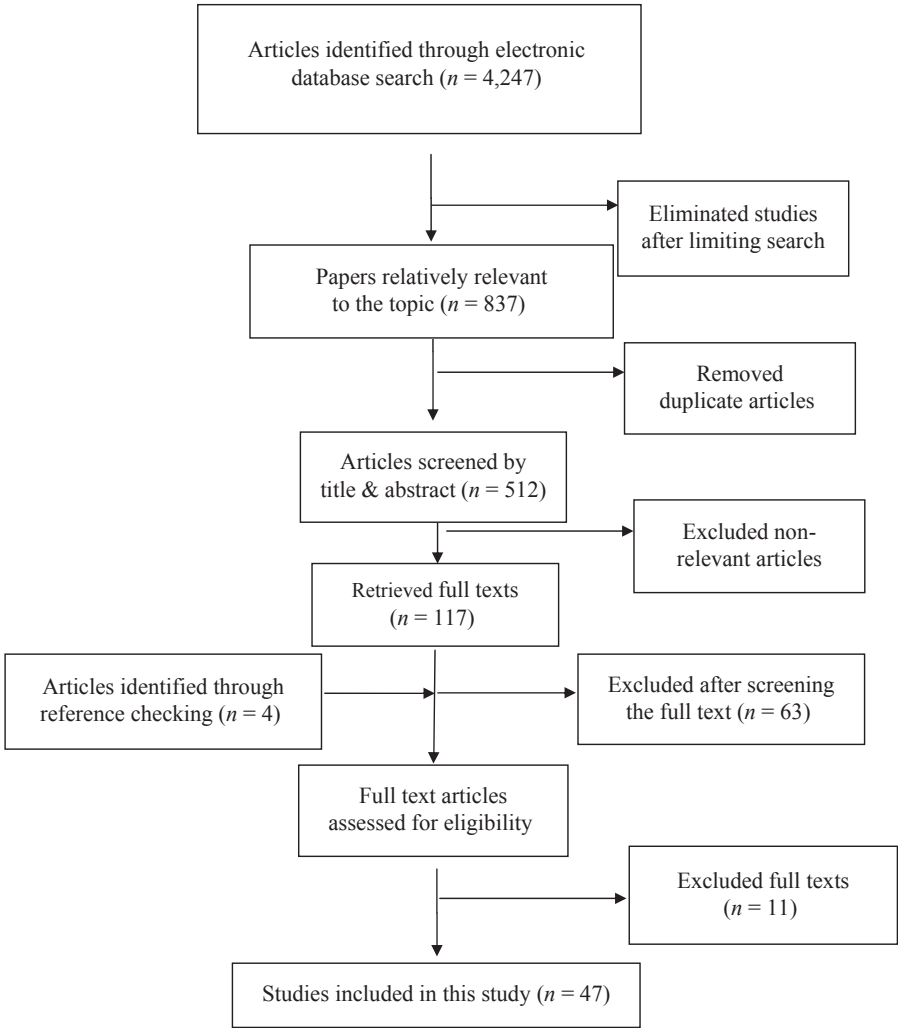

Figure 1. Literature search and review flowchart for selection of primary studies.

Table 1. Distribution of characteristics of primary studies included in meta-analysis.

				Gender			Area residence		Job			High Risk behavior		Clinical sign			Age		
Id	First author (Ref)	Publication year	Sample size	Male	Female	Sex ratio	Urban	Rural	Ranchers and farmers	Student	Housewife	Animal contact	Unpasteurized dairy	Fever	Joint pain	Sweating	Average	least	high
1	Hasanzadeh [20]	2013	139	68.0	32.0	2.09	49.6	50.4				59.71	69.06						11–20
2	Almasi-Hashiani [21]	2011	907	61.0	39.0	1.56	21.3	78.7	36.30	12.80	34.60						37.20		
3	Haddadi [22]	2006	415	47.7	52.5	0.91	84.3	15.7			35.66	17.10	76.38	67.22	61.44	73.25	35.50	<20	20–40
4	Sharifi-Mood [23]	2007	181	53.0	47.0	1.13	24.6	75.4	38.0		4.00		29.0	50.00	43.0		39.00		
5	Sahargahi [24]	2014	458	44.4	55.6	0.80	10.0	90.0	33.10		39.40						34.70		
6	Ghasemi [25]	2003	1,591	51.5	48.5	1.06	22.0	78.0	16.50	19.50	41.70	10.60	36.70						15–19
7	Ayazi [16]	2012	175	61.0	39.0	1.56	43.0	57.0		50.00		58.00	65.0	78.00	22.50	44.0		<1	7–12
8	Eini [15]	2012	230	56.5	43.5	1.30	23.8	72.6				39.70	60.30	77.40	70.00	46.90	40.84	>80	21–60
9	Kassiri [4]	2013	43	65.1	34.9	1.87	17.1	82.9	20.90	6.70	30.20	20.90	79.10				33.34	0–4	15–24
10	Shoraka [7]	2010	64	68.8	31.2	2.20	9.4	90.6	12.50	15.60	26.60	82.80	23.40	62.50	56.20	32.80	30.70		
11	Karami [26]	2009	194	45.0	55.0	0.83	37.0	63.0	17.53	16.49	39.69	60.00	40.00					70–79	10–29
12	Rajabzadeh [27]	2013	1,310	55.3	44.7	1.24	28.5	71.5	19.80	13.10	36.30	77.80	60.89						
13	Golsha [28]	2011	77	74.0	26.0	2.85	27.8	72.2				27.20	53.30	83.10					
14	Fallah [29]	1998	1,148	54.0	46.0	1.20												>50	<25
15	Afsharpaiman [30]	2008	40	65.9	34.1	2.10	61.0	39.0					65.90	77.40	50.0	52.30	7.31		
16	Beheshti [31]	2001	130	61.0	39.0	2.51	45.0	55.0				58.50	49.00	98.00	72.0	92.0	30.00		
17	Bokaie [32]	2009	460	37.7	62.3	0.61			18.75		29.53								10–29
18	Mamishi [33]	2005	44	65.9	34.1	1.93	61.0	39.0					65.90	77.40	52.00	52.30	7.31		
19	Bokaie [34]	2009	176	54.5	45.5	1.20	16.0	84.0										<19	20–40
20	Ebrahimpour [35]	2012	377	54.4	45.6	1.19	25.7	74.3	5.57	18.22	40.31		23.07					<10	>50
21	Hosseini [36]	2009	115	68.7	32.2	2.11			34.80	13.90	23.50	80.90	89.60	86.10	77.40	73.90	29.40	<2	17–35
22	Farahani [37]	2011	3,880	60.0	40.0	1.50	28.0	72.0										>70	10–19
23	Bahador [38]	2012	40	52.5	47.5	1.11			47.50				100.0				40.00	>64	8–16
24	Kamran [39]	2011	126	57.9	42.1	1.38	27.0	73.0					37.70	40.50	13.50		41.29		50–59
25	Almasi [40]	2012	210	69.9	30.1	2.32						46.20	52.90		61.40		34.30	>60	15–30
26	Soleimani [41]	2012	5,732	54.9	45.1	1.22	14.4	85.6				80.00	86.40				30.90	<5	15–25
27	Ettehad [42]	2007	51	76.5	23.5	3.25	34.0	66.0					62.00	84.20	44.00	60.20	6.25		
28	Soleimani [43]	2010	42	68.8	24.4	2.82	33.0	67.0				33.30			83.0	76.40		<5	10–15
29	Maleki [44]	2015	492	52.3	47.7	1.10	19.0	81.0	8.30	15.00	39.40							>70	25–30
30	Moradi [18]	2006	3,880	52.1	47.9	1.09	18.2	81.8	20.80	20.60	39.40	62.10					30.03	45–54	16–44
31	Zeinalian Dastjerdi [45]	2012	1,996	32.8	67.2	0.49	32.0	68.0	18.10	15.20	25.70								15–20
32	Ghaffarpour [46]	2007	15	60.0	40.0	1.50	33.0	67.0						33.30	53.30		37.70		
33	Haj Abdolbaghi [47]	2001	505	63.6	36.4	1.74	59.5	40.5	34.25				66.70	65.0					10–20
34	Sasan [48]	2012	82	60.0	40.0	1.21	29.8	70.2				76.0	91.60	5.0	79.70		8.02		

35 Hasanjani Roushan [49]	2004	469	56.9	43.1	1.32	39.2	60.8	11.30			22.40	67.0	53.70	76.10	36.90		
36 Pourahmad [50]	2012	168	68.5	31.5	2.17			4.80		7.70					28.51	≥60	10–29
37 Hajia [51]	2009	809	61.2	38.8	1.58			20.51	17.20	26.46		83.80	80.34	40.30		>80	11–20
38 Moumen Heravi [52]	2007	590	59.0	41.0	0.61	68.4	31.6					19.20	70.0	59.70		≥60	20–39
39 Khalili [53]	2014	32	75.0	25.0	3.00							39.00	41.0				
40 Mohammadian [54]	2014	554	64.4	35.6	1.81	9.7	90.3								34.30	<10	20–30
41 Noroozi [55]	2012	1,253	53.0	47.0	1.13	28.0	72.0	16.50	11.50	35.50						<10	20–29
42 Esmaeilnasab [56]	2007	1,059	50.8	49.2	1.03	10.0	90.0	27.10	12.70	44.20					34.05	>55	25–44
43 Hamzavi [57]	2014	777	52.6	47.4	1.11	12.4	87.6	32.30		37.80						≥70	20–29
44 Sawadkohi [58]	2002	116			1.60							97.0		44.0		6–24	60–144
45 Fanni [59]	2013	34	65.0	35.0	1.86						15.00	74.00	65.0	59.0	6.88	10–14	2–5
46 Mugahi [60]	2014	81	59.3	40.7	1.45	46.9	53.1	12.30		18.50		85.20	42.0	38.30	38.10	<20	>40
47 Dehnavi [61]	2015	305	53.4	46.6	1.15			8.20	20.70	37.00		56.10	81.0	18.40	36.66	>71	11–20

irrelevant ones, 58 studies were controlled through assessment checklist and 11 articles were omitted. Finally, 47 articles were selected (Figure 1).

In 47 studies selected for meta-analysis, we assessed the epidemiological features of 31,572 patients with Malta fever in Iran. Of 47 studies selected for this structural review, 42 articles followed analytical–descriptive methods and the remaining five articles did not follow any specific method. The publication year varied from 1998 to 2015 (Table 1).

Variables such as gender, residence, age, occupation, high-risk behavior, and clinical signs were assessed. Table 2 shows the frequency of the variables.

3.1. Gender

The gender distribution of patients with Malta fever was reported in 46 articles, which demonstrated that Malta fever in men varied from 32.8% (in Zeinalian Dastjerdi et al's [45] study) to 76.5% (in Ettehad et al's [42] study), and in women, it varied from 23.5% (in Ettehad et al's [42] study) to 67.2% (in Zeinalian Dastjerdi et al's [45] study). The ratio of male/female patients with Malta fever in 41 of 47 studies was > 1 and it varied from 0.49 (in Zeinlian Dastjedri's study) to 3.2 (in Ettehad et al's [42] study). Using meta-analysis, the frequency of Malta fever in men and women in Iran was estimated to be 57.6% (55.02–60.1%) and 42.3% (39.8–44.9%; Figures 2 and 3).

3.2. Residency

Thirty-six articles reported the residential status (rural and urban) of people with Malta fever. The prevalence of Malta fever in accordance with residential status varied from 9.4% (in Shoraka et al's [7] study) to 84.3% (In Haddadi et al's [22] study) in urban areas and 15.7% (in Haddadi et al's [22] study) to 90.6% (Shoraka et al's [7] study) in rural areas. The results of meta-analysis demonstrated that 31.4% (26.7–36.3%) and 68.4% (63.6–73.2%) of patients with Malta fever in Iran lived in urban and rural areas, respectively.

3.3. Age

The mean age of people with Malta fever was reported in 26 studies, which varied from 6.25 years (in Ettehad et al's [42] study) to 41.29 years (in Kamran et al's [39] study). The 10–40 years age group was the most frequent group with Malta fever in Iran. Age has not been estimated by using meta-analysis so far. The reason is that the standard error could not be calculated as a result of information deficiency in primary studies.

3.4. Occupation

The frequency of Malta fever among ranchers and farmers was reported in 24 studies, which varied from 4.8% (in Pourahmad et al's [50] study) to 47.5% (in Bahador et al's [38] study). The frequency of Malta fever among students was reported in 16 studies, which

Table 2. Estimation of frequency of brucellosis by epidemiological and clinical factors in Iran using meta-analysis.

Variables	Frequency (95% CI)	Heterogeneity		
		Q	I^2 (%)	p
Male	57.6 (55.02−60.1)	790.02	94.3	<0.001
Female	42.3 (39.8−44.9)	795.8	94.3	<0.001
Urban	31.4 (26.7−36.3)	3,308.9	98.9	<0.001
Rural	68.4 (63.6−73.2)	3,311.8	98.9	<0.001
Ranchers & farmers	20.8 (17.4−24.2)	740.4	96.9	<0.001
Students	16.9 (14.5−19.4)	210.5	92.9	<0.001
Housewife	31.6 (27−36.2)	862.2	97.6	<0.001
Animal contact	50.4 (35.6−65.2)	6,575.3	99.7	<0.001
Unpasteurized dairy	57.1 (46.4−67.9)	3,684	99.3	<0.001
Fever	65.7 (53.7−77.8)	2,832.04	99.2	<0.001
Joint pain	58.1 (49.5−66.6)	788.5	97.3	<0.001
sweating	55.3 (44.4−66.2)	849.6	98.1	<0.001

CI = confidence limit.

varied from 6.7% (in Kassiri et al's [4] study) to 50% (in Ayazi et al's [16] study). The frequency of Malta fever among housewives was reported in 22 studies, varying from 4% (in Sharifi-Mood's study) to 44.2% (in Esmaeilnasab et al's [56] study). The results of occupation meta-analysis were as follows: 20.8% (17.4−24.2%) of the patients with Malta fever in Iran were ranchers and farmers; 16.9% (14.5−19.4%) were students, and 31.6% (27−36.2%) were housewives.

3.5. High-risk behavior

Eighteen articles reported contact with animals and breathing in barns and stable environments among patients with Malta fever, which varied from 10.6% (in Ghasemi et al's [25] study) to 82.8% (in Shoraka et al's [7] study). The results of meta-analysis indicated that direct contact with animals in 50.4% (35.6−65.2%) of patients was reported as the cause of the disease. Twenty-six articles reported the frequency of using unpasteurized dairy products among patients with Malta fever; the results of which varied from 22.4% (in Hasanjani Roushan et al's [49] study) to 100% (Bahador et al's [38] study). The results of meta-analysis indicated that using unpasteurized dairy products was reported as the cause of the disease in 57.1% (46.4−67.9%) of the patients.

3.6. Clinical signs

Regarding the clinical signs, the frequency of fever was reported in 23 studies, which varied from 5% (in Sasan et al's [48] study) to 98% (in Beheshti et al's [31] study). The frequency of joint pain was reported in 22 studies, which varied from 13.5% (in Kamran et al's [39] study) to 83% (in Soleimani et al's [41] study). The frequency of sweating was reported in 17 studies, which varied from 18.4% (in Dehnavi et al [61]'s study) to 92% (in Beheshti et al's [31] study). According to the meta-analysis results, the frequency of fever, joint pain and sweating was 65.7% (53.7−77.8%) and 55.3% (44.4−66.2%), respectively.

4. Discussion

The current study investigated the epidemiology, clinical features and high-risk behavior among patients with Malta fever through a meta-analysis. The results revealed that 57.6% of the patients were male and 42.3% were female, which is a significant difference due to the 95% confidence interval and nonoverlapping. Of the patients studied, 31.4% and 68.4% resided in urban and rural areas, respectively, which was a significant difference. With respect to occupation, about 21% of the patients were ranchers and farmers, about 17% were students, and 31.6% were housewives. About 50% of the patients had contact with cattle and 57% used unpasteurized dairy products. Regarding the clinical signs, 58.1% of the patients had joint pain. Most of patients were aged 10−40 years.

Malta fever is more prevalent in men than women, therefore, gender is introduced as a risk factor in some studies [5,62,63]. In a study conducted by Donev et al [64], it was demonstrated that Malta fever was more prevalent among villagers than people residing in urban areas due to having contact with infected animals and using unpasteurized products. A study conducted in Saudi Arabia indicated that brucellosis in rural areas was more prevalent as compared to urban areas [65]. Another study of Malta fever among children aged < 15 years in Jordan demonstrated that living in villages increased the chance of being infected with brucellosis [66].

The age range of patients with Malta fever in most studies was consistent with our research [65,67−70]. In

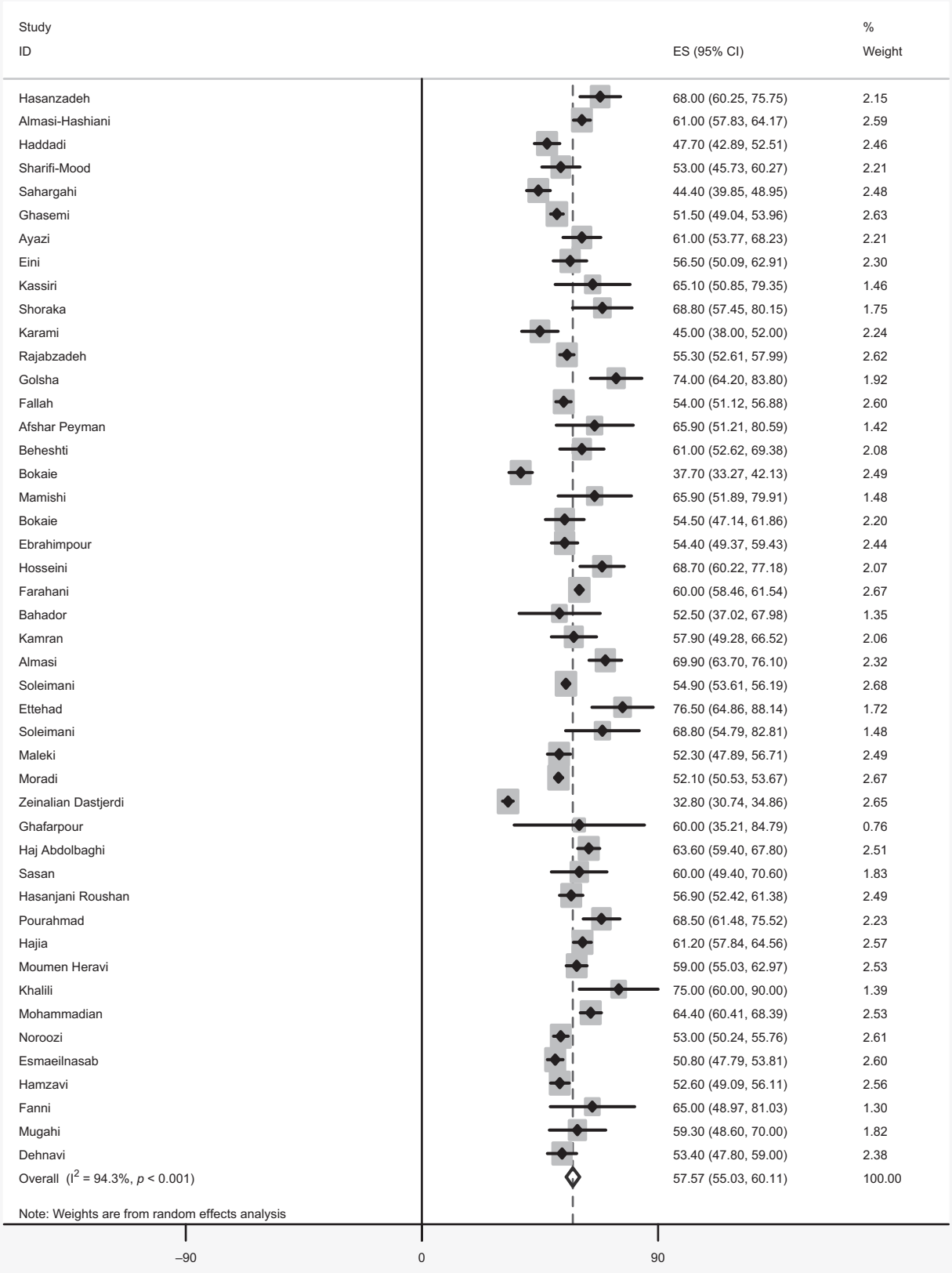

Figure 2. Pooled estimate of brucellosis prevalence in Iranian men.

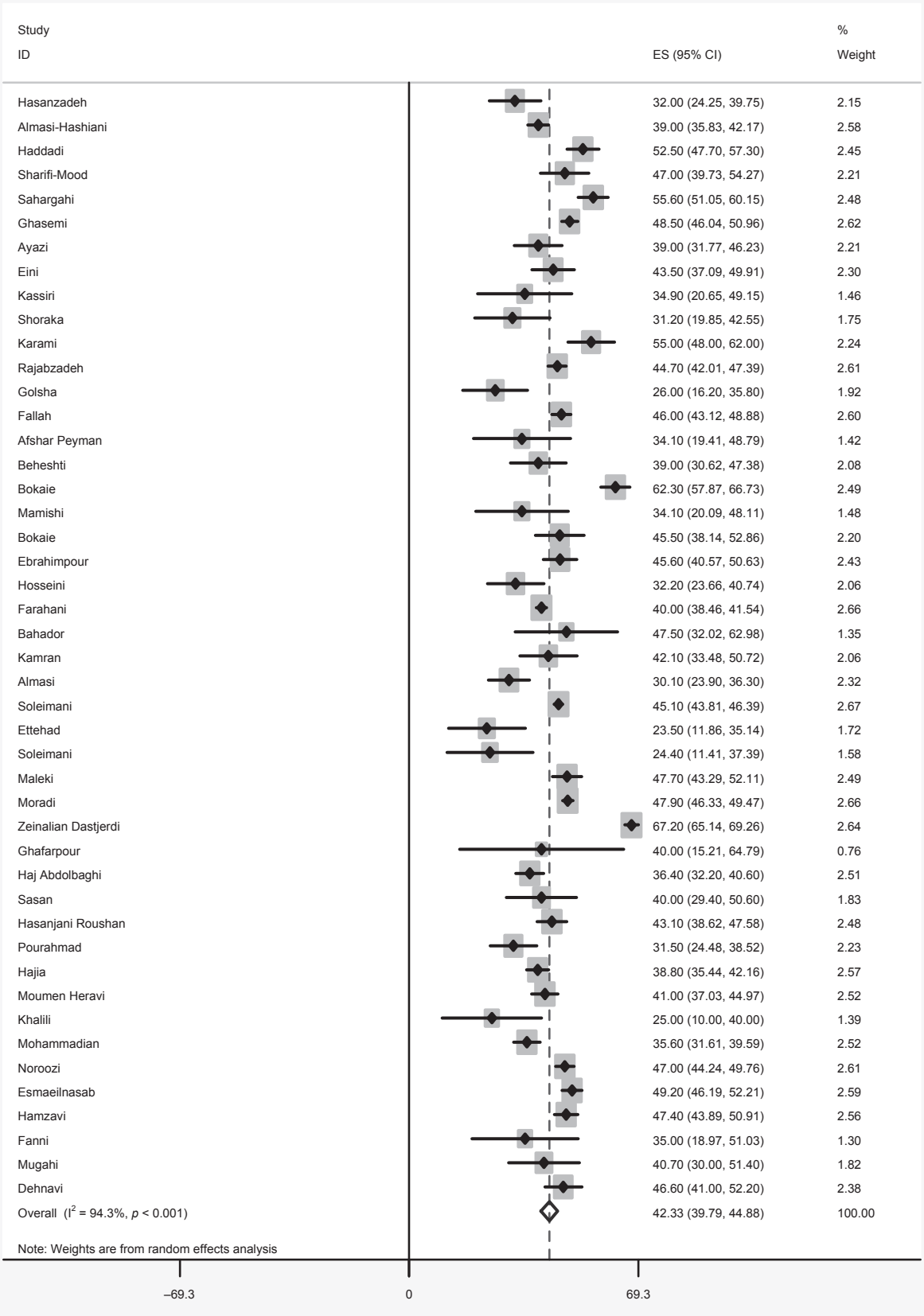

Figure 3. Pooled estimate of brucellosis prevalence in Iranian women.

a study conducted by Mohammad Al-Sekait [71], high-risk behavior, direct contact with infected cattle, and using unpasteurized dairy products were considered as the most important factors affecting Malta fever in Madina. In a case–control study in Yemen, Al-Shamahy et al [72] reported that farmers and inhabitants who consumed unpasteurized dairy products were more affected with Malta fever than the control group. In yet another study carried out in a province of Saudi Arabia, the most infected occupational group included housewives, farmers, ranchers, and students [65]. Husseini et al [6] found that Palestinian farmers were more susceptible to being infected with Malta fever as compared with other occupations. The results of a study conducted in Oman revealed that consuming infected milk and contact with infected cattle were the main causes of Malta fever [73]. In a study on inhabitants of eight villages in Greece, it was demonstrated that using unpasteurized dairy products, being in the risky occupation group (i.e., ranchers and slaughterhouse workers), and having contact with infected animals were among the factors leading to more cases of Malta fever [74]. A study carried out in Northern Egypt reported that people who had contact with animals were more susceptible to Malta fever than those with no animal contact [70]. Earhart et al [75], in their study on Samarqand in Uzbekistan, found that Malta fever was more prevalent among people whom had more contact with cattle and those who used more dairy products.

In a study conducted in Turkey, using unpasteurized dairy products, raising cattle, and having risky occupations (veterinarians and butchers) were considered as factors affecting Malta fever, and fever and joint pain were reported as the most common symptoms of this disease [76]. Other studies carried out in Turkey also report fever, sweating, and joint pain as the most prevalent clinical signs [77,78]. In a systematic review study conducted by Dean et al [79], it was indicated that fever, sweating, and joint pain were the most prevalent symptoms of Malta fever.

In Macedonia, Bosilkovski et al [80] found that most people with Malta fever, had a history of direct animal contact and suffered mostly from joint pain and sweating.

Heterogeneity was a limitation of the current research. To resolve this, the research used a random-effect model. Another limitation was that epidemiological features and high-risk behavior, such as article selection criteria, were scattered and, therefore, they were not measured comprehensively in all articles.

The present study revealed that the frequency of male patients with brucellosis was considerably more than female patients. The number of patients with brucellosis in rural areas was significantly more than in urban areas. Most patients were economically active in society. High-risk behavior, unprotected contact with animals, and using unpasteurized dairy products were among the most significant factors determining brucellosis infection in Iran. A high incidence of the disease in some occupational groups, such as ranchers, farmers, and housewives, and rural areas (compared to urban areas), is probably due to the frequency of high-risk behavior. Fever, joint pain, and sweating were detected among most patients with Malta fever.

Conflicts of interest

The authors declare that there was no conflict interest.

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