PLOS ONE

Is latent tuberculosis infection challenging in Iranian health care workers? A systematic review and meta-analysis

--Manuscript Draft--

Manuscript Number:	PONE-D-19-18112
Article Type:	Research Article
Full Title:	Is latent tuberculosis infection challenging in Iranian health care workers? A systematic review and meta-analysis
Short Title:	LT BI among HCWs in Iran
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Keywords:	Latent Tuberculosis; Health Personnel; Iran
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Is latent tuberculosis infection challenging in Iranian health care workers?

A systematic review and meta-analysis

Running title: LT BI among HCWs in Iran

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Abstract:

Background: Latent tuberculosis infection (LTBI) has been changed to one of the challenges of health care workers (HCWs) in low middle-income countries.

Method: Search strategies that were lead through Persian)national(databases include SID, Barakat knowledge network system; Irandoc, Magiran; Iranian national library. The international database was Web of science, Scopus, PubMed/MEDLINE, OVID, EMBASE, the Cochrane library, and Google Scholar search engine. The Persian and the English languages were used as the filter in national and international databases, respectively. Searching was done through MeSH terms. The search terms were conducted till January 01, 2019.

Results: The prevalence of LTBI in Iranian HCWs, based on the PPD test was (27.13% [CI95%: 18.64-37.7]). The highest prevalence of LTBI in HCWs were estimated (41.4 % [CL95%: 25.4-59.5] in the north, and (33.8% [CI95%: 21.1-49.3]) in the west of Iran. The lowest prevalence of LTBI was evaluated (18.2% [CI95%: 3.4-58.2]) in the south of Iran. The prevalence of LTBI in HCWs who had work-experience more than 20 years old were estimated (20.49% [CI95%: 11-34.97]). In the PPD test, the prevalence of LTBI in HCWs who had received the Bacille Calmette–Guérin (BCG) was estimated (15% [CI 95%: 3.6-47.73]). While, in the QFT, the prevalence of LTBI in HCWs in non-vaccinated was estimated (25.71% [CI95%: 13.96-42.49]).

Conclusions: This meta-analysis shows the highest prevalence of LTBI in HCWs in the north and the west of Iran due to neighboring countries like Azerbaijan and Iraq, respectively. Hence, Iranian HCWs do not fully understand the isolation and personal protection. We also found that BCG was not able to protect Iranian HCWs from TB infections, completely.

Keywords: Latent Tuberculosis; Health Personnel; Iran

1. Introduction:

Latent tuberculosis infection (LTBI) is an immune response to *Mycobacterium tuberculosis* (Mtb) antigens without symptoms of active tuberculosis (TB) [1]. Mtb is able to colonize inside the alveolar macrophages and finally form granuloma. Mtb is ingested by phagocytosis by resident alveolar macrophages and tissue dendritic cells (DC) [2, 3]. The immune cells contribute and the pathological mark of TB, the granuloma, is formed. In the granuloma, macrophages differentiate into epithelial cells or foamy macrophages, or fuse to form giant cells, and become surrounded by lymphocytes, fibroblasts and extracellular matrix proteins. In such conditions, the Mtb will be surviving until the granuloma fails due to immunosuppression [4, 5]. Mtb use the granuloma as they are effective at initial infection level since they recruit new macrophages to allow the spread of infection between host cells [6]. At this stage, the LTBI is formed in the patient's body.

[7]. There are several reports of LTBI outbreaks in Iran; however, the highest prevalence of LTBI has been reported to be 82% in Sistan-Baluchistan province [8]. The risk of tuberculosis in health care workers (HCWs) is estimated to be twice as high in the general population, in high-income countries, and five times higher than the general population in countries with a low and middle income [9, 10].

In addition, one of the challenges in many countries is the transfer of tuberculosis from patients admitted to the hospital to HCWs [10]. Most importantly, the transfer of resistant Mycobacterium tuberculosis strains from admitted patients to HCWs has increased the importance of the subject [11].

According to the findings, direct exposure to HCWs in patients with tuberculosis, direct contact with phlegm specimens and blood products of suspected tuberculosis patients, and long hours of work in high-risk places increases the risk of tuberculosis infection [12, 13]. This means that direct contact is one of the most important and worrisome factor in the

transmission of tuberculosis to HCWs [10-12, 14]. Work experience, age [15], occupational status [16], the use of personal protective equipment, ventilation, hospital Infection Control Unit and infection control in isolation rooms can affect LTBI outbreaks in HCWs [9-12]., T [17]. To diagnose LTBI, the Mantoux tuberculin skin test (TST) and QuantiFERON-TB Gold (QFT) are used [18]. Studies have shown that QFT has a higher sensitivity and specificity in detecting LTBI [19, 20]. However, some researchers believe that QFT is not superior to TST in detecting LTBI [21-23].

The early detection of LTBI in controlling, treating and preventing Mtb is a key element in patients. So that preventive treatment can reduce the risk of active tuberculosis in patients by up to 90% [24]. So far, systematic review and meta-analysis has not been conducted to evaluate the prevalence and risk factors of LTBI among HCWs in Iran. In Iran, the Centers for Disease Control and Prevention (CDC) do not control the Mtb as a regular program, however, reports of LTBI outbreaks in HCWs attracts a high controversy [25]. Due to the highest level of evidence and an essential role in evidence-based decision-making of meta-analysis studies [26, 27], this study estimated the prevalence and risk factors of LTBI among HCWs in Iran which can have vital information for policy-makers and planning at the country level.

2. Materials and methods

2.1. Study Protocol

This is the first study that was conducted based on the meta-analysis of observational studies according to epidemiology guidelines [27], and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (S1 File) [28]. The study was achieved based on five steps; design and search strategy; collecting original articles; evaluating inclusion and exclusion criteria, and finally qualitative evaluation and statistical analysis of data. Two independent researchers)MH. YK& A.J(evaluated the data. The disagreements were solved by consensus between the team, and a bacteriologist (H.S.E). The review protocol was registered in PROSPERO :International Prospective Register of Systematic Reviews) https://www.crd.york.ac.uk/PROSPERO/) Identifier: CRD42018117682 [29, 30] (S2 File).

2.2. Search strategy

In order to maximize its sensitivity, search strategy was six lead through Persian (national) databases, including scientific information database (SID))http://www.sid.ir/), Barakat knowledge network system)http://health.barakatkns.com), Iranian research institute for information science and technology)IranDoc( )https://irandoc.ac.ir), Magiran)http://www.magiran.com), Iranian national library)http://www.nlai.ir/). The international databases, including web of science, Scopus, PubMed/MEDLINE, OVID, EMBASE, the Cochrane Library)Cochrane Database of Systematic Reviews(,and Google Scholar search engine. he Persian and the English T languages were used as the filter in national and international databases, respectively. The search terms were adapted to international databases. To search a combination of words, Boolean operators) AND& OR(were used. hing was done through medical Searc subject heading)MeSH(terms. The search terms were conducted without any time limitation

till January 01, 2019. The authors were then independently analyzed the manuscript contained in the title and abstract. For instance, PubMed search formula was provided in the appendix.

2.3. Inclusion and exclusion criteria

2.3.1. Inclusion criteria based on PICO (related to Evidence-Based Medicine) [31, 32]

(1) **P**opulation: This study was been concentrated on the population of HCWs with LTBI who were residents in the geographic regions of Northern, Southern, Eastern, Western, center, and capital city of Iran. ;)2(**I**ntervention: The exposure were the laboratory tests (Interferon-gamma (IFN-γ) release assay (IGRA), and tuberculin skin tests)TST((of which confirmed LTBI among HCWs in Iran. ;)3(**C**omparison: A population of HCWs who did not have signs of active TB disease and did not feel illness.; (4) **O**utcome: Estimate the overall prevalence and risk factors of LTBI infection among HCWs in Iran.

2.3.2. Exclusion criteria

Review articles, letters, editorial, case reports, conference papers, and comments were excluded. The studies of which did not have a focus on the prevalence of LTBI in Iranian HCWs, duplicated papers, non-English full papers, non-Persian full papers, and non-assessable full-text papers were excluded. Likewise, the populations other than Iranian HCWs were excluded.

2.4. Latent TB detection criteria

2.4.1. The Mantoux tuberculin skin test (TST)

To the Mantoux tuberculin skin test (TST), purified protein derivative (0.1 Ml) is used [33-35], and the induration at TST site is measured 72 hours later. TST reaction of ≥ 5 mm of induration is classified as negative but is considered as positive in patients receiving corticosteroid or patients with Acquired Immunodeficiency Syndrome (AIDS), diabetes

mellitus, lymphoma, and leukemia. The induration of ≥10 mm is classified positive in; recent immigrants (< 5 years) from high-prevalence countries; residents and employees of high-risk congregate settings; mycobacteriology laboratory personnel; persons with clinical conditions that place them at high risk. The induration of ≥15 mm is considered positive in any person, including persons with no known risk factors for TB. Two-step testing methods were used for health care workers and nursing home residents [33-35].

2.4.2. Interferon-gamma release assays

Interferon-gamma release assays (IGRAs) show how the immune system reacts to the Mycobacteria that cause TB [36]. The IGRA has been approved by the U.S. Food and Drug Administration (FDA). Positive IGRA means that the person has been infected with TB bacteria. Negative IGRA means that the person's blood did not react to the test and that latent TB infection or TB disease is not likely. IGRA is the preferred method of TB infection testing for people who have received the Bacille Calmette–Guérin (BCG) [30, 36-39].

2.5. Selection of studies

During the selection stage, duplicated studies were removed by the EndNote™ software Ver. X9 (Clarivate Analytics company). In the skimming and screening stage, co-authors, journals, and publishing years were evaluated by two experts based on inclusion and exclusion criteria (the eligibility stage), independently. The disagreements between the two were resolved through an expert bacteriologist (Figure 1).

Fig 1. A flow diagram (Stacked Venn) following the PRISMA (Depicted by MH-YK).

2.6. Quality appraisal

In this stage, the irrelevant studies were excluded, and then the quality of each study was evaluated. To quality appraisal, the Newcastle-Ottawa Scale (NOS) checklist (S3 File)[40] was applied whichdetermined the quality of these studies based on three levels of scoring.

The score of five or less defined a poor quality study; the score of five or six distinguished as the medium quality study, and the score of seven or eight determined as the high-quality study. Finally, the medium to high-quality studies were included in the data analysis (Fig 1).

Fig 1. A flow diagram (Stacked Venn) following the PRISMA (Depicted by MH-YK).

2.7. Data extraction

The enter terms were author's names, province, geographical regions, year of publishing, sample size, age ,gender ,history of BCG ,history of exposure with tuberculosis ,history of tuberculosis disease ,laboratory diagnosis tests, job experience, duration of employment, workplaces, single-step or two-step TST, and history of hospitalization. The author's name, institution, and the journal name were blinded, and then data was extracted through two researchers (MH.YK & A.J), independently. Only if necessary, the additional information/raw data was collected by phone call, mailing, or fax.

2.8. Statistical analysis

The prevalence of LTBI in HCWs was considered as a binomial distribution probability, and the variance was calculated by a binomial distribution. To evaluate its heterogeneity, the Cochran test (Q) and I^2 index were used[1, 41, 42]. The subgroup analysis was performed based on province, single-step or two-step TST, laboratory diagnosis tests, job, gender, history of TB disease, history of TB exposure, history of BCG, and geographical regions. Sensitivity analysis was also achieved to evaluate the impact of each study, based on the results of the overall prevalence of LTBI in Iranian HCWs. The Begg's test and Egger's test were carried out using a funnel plot to examine publication bias. Data analysis was examined by the Comprehensive Meta-Analysis Ver .2)Englewood ,NJ 07631, USA((,and level of significance was considered as $p<0.05$.

3. Results:

3.1. Study characteristics and methodological quality

In the primary search of study, 421 studies were found. After skimming and screening, 20 (4.75%) studies were eligible according to inclusions and exclusions criteria [43-62]. The total sample size was calculated 6453 Iranian HCWs (Fig 1) (S1 Table.(

Fig 1. A flow diagram (Stacked Venn) following the PRISMA (Depicted by MH-YK).

3.2. The overall prevalence LTBI in HCWs

The prevalence of LTBI in HCWs, based on the PPD test (48 hours) was (27.13% [CI95%: 18.64-37.7]) (Fig 2), and based on the QFT test was (16.92% [CI95%: 9.7-27.84]) (Fig 3). The prevalence of LTBI was estimated (12.11% [CI95%: 4.53-28.57]) in Iranian HCWs who had negative TST reaction (48 hours) in the first week (Fig 4). The prevalence of induration at TST site (48 h) was estimated <4 mm in (43.74% [CI 95%: 28.19-60.63]), 5-9 mm in (17.52% [CI 95%: 9.73-29.5]), 10-15 mm in (14.55% [CI 95%: 8.87-22.93]) and >15 mm in (13.4% [CI 95%: 8.59-20.31]) (S1 Fig).

Fig 2. The prevalence subgroup analysis (Forest plot - Random effect model) based on TST/PPD induration diameter (48 hrs.) in HCWs with LTBI.

Fig 3. The prevalence subgroup analysis (Forest plot - Random effect model) based on QFT in HCWs with LTBI.

Fig 4. The prevalence subgroup analysis (Forest plot - Random effect model) based on TST/PPD induration diameter after one week in HCWs with LTBI.

3.3. The prevalence of LTBI in Iranian HCWs based on geographical region of Iran

The highest prevalence of LTBI in HCWs was estimated (41.4 % [CL95%: 25.4-59.5] in the north, and (33.8% [CI95%: 21.1-49.3]) in the west of Iran. The lowest prevalence of LTBI was evaluated (18.2% [CI95%: 3.4-58.2]) in the south of Iran. These results showed a

significant relationship between LTBI prevalence in HCWs and the geographic location in Iran ($p < 0.0001$) (S2 Fig) (Fig 5).

Fig 5. Distribution of LTBI in Iranian HCWs based on geographical classification (Random effect model).

3.4. Sensitivity analysis and cumulative meta-analysis

Sensitivity analysis of prevalence of LTBI in Iranian HCWs was estimated with a 95% confidence interval. It showed that there is no significant effect on the overall prevalence of LTBI in Iranian HCWs (Fig 6). The overall prevalence of LTBI in Iranian HCWs based on the publication year was estimated by cumulative meta-analysis and represented in (S3 Fig).

Fig 6. Sensitivity analysis to prevalence of LTBI in Iranian HCWs (one study removed test)

3.5. Meta-regression

The prevalence of publishing manuscripts about identification of LTBI in HCWs by the PPD test (48 hours), has decreased in Iran. There was however no significant relationship. (Mixed effects regression (Method of moments); Slope = -0.1898(SE = 0.068, (95% CI: -0.323– -0.056)), Intercept = 381.14 (SE = 137.43, (95% CI: 111.78–650.5)), P = 0.10653) (Fig 7).

Fig 7. Meta-regression of LTBI in Iranian HCWs according to publishing year of studies (method of moments).

3.6. The prevalence of LTBI in HCWs based on term of employment

The prevalence of LTBI in Iranian HCWs with more than 10 years old work-experience was evaluated 51%. The prevalence of LTBI in HCWs with less than 10 years old work-experience was estimated 29.30% in the PPD test. The prevalence of LTBI in HCWs with more than 20 years old work-experience was calculated (20.49% [CI95%: 11-34.97]), which

showed a significant relationship between the term of employment in QFT (P <0.0001) (S4 Fig).

3.7. The prevalence of LTBI in Iranian HCWs based on occupation and wards

The prevalence of LTBI in assistant nurses was estimated 45.76% [CI 95%: 33.51-58.55], in physicians was evaluated 44.99% [CI95%: 33.37-57.17], in ward nurses was calculated 39.4% [CI95%: 17.63-66.39], and in service workers was estimated 36.43% [CI95%: 19.51-57.53] based on PPD test. The prevalence of LTBI in both nurses and TB service workers was higher than other occupations based on QFT (Fig 8).

Fig 8. The prevalence subgroup analysis of occupational (Forest plot - Random effect model) based on PPD (A), and QFT (B) in HCWs with LTBI.

The prevalence of LTBI in the infectious ward was estimated (52.09% [CI95%: 43.92-60.14]), and in the internal ward was evaluated (50% [CI95%: 34.22-65.78]. The lowest prevalence of LTBI was estimated in the infectious wards based on QFT. There was a significant relationship between the prevalence of LTBI in HCWs, and hospital wards (p <0.0001) (Fig 9).

Fig 9. The prevalence subgroup analysis of ward (Forest plot - Random effect model) base on PPD (A), and QFT (B) in HCWs with LTBI.

3.8. The prevalence of LTBI in HCWs based on gender and age

The prevalence of LTBI was estimated at 42.16% [CI95%: 26.41-59.69] in male Iranian HCWs based on the PPD test. The prevalence of LTBI in Iranian HCWs and type of gender based on PPD test (P <0.051). In QFT, however, a significant relationship was showed between the prevalence of LTBI in HCWs, and the gender (P <0.0001) (S5 Fig).

The prevalence of LTBI in HCWs who were more than 40 years old was estimated 44% [CI 95%: 26.47-63.16] in the PPD test.

The prevalence of LTBI in Iranian HCWs aged 30 years old was estimated 22.52% [CI95 %: 3.7-68.34] in the QFT. In both PPD test and QFT, it was evaluated that there was no significant relationship between the prevalence of LTBI in HCWs, and age of HCWs (P <0.0001) (S6 Fig).

3.9. The prevalence of LTBI in HCWs based on the history of tuberculosis contact and the tuberculosis clinical symptoms

The results showed that 30.15% [CI 95%: 11-60.13] of Iranian HCWs directly contacted to patients with tuberculosis. The results also showed that 6.9% [CI 95%: 2.36-18.55] of Iranian HCWs had active tuberculosis symptoms (S7-8 Fig).

3.10. The prevalence of LTBI in HCWs based on the "BCG"

The prevalence of LTBI in Iranian HCWs who received the BCG was estimated (15% [CI 95%: 3.6-47.73]) based on the PPD test. While the prevalence of LTBI in Iranian HCWs who did not receive the BCG was estimated at 25.71% [CI95%: 13.96-42.49] based on the QFT. In both PPD, and QFT, there was a significant relationship between those who did and those who did not receive the vaccine (S9 Fig).

3.11. Publication bias

The publication bias in this study was evaluated by Begg's and Egger's tests. The publication bias by Begg's test was calculated 0.06, and the Egger's test was calculated 0.028. The probability of the publication bias in this study was significant (S10 Fig).

4. Discussion:

This study is the first systematic review and meta-analysis of latent tuberculosis outbreak (LTBI) been carried out in health care workers (HCWs) in Iran. According to results of the current meta-analysis, the prevalence of LTBI in HCWs in Iran is estimated at 27.1% [1]. Among the low- and middle-income countries, the prevalence of LTBI in Kenya [63], Zimbabwe [64], Russia [65], Brazil [66], Vietnam [67], Rwanda [68], China [69] and South Africa [70] has been higher than in Iran [1]. The prevalence of LTBI in HCWs Italy [71], Norway [72] and India [73] is reported to be equal to or less than Iran. Iran is a TB endemic country [25] and the treatment of latent tuberculosis is usually done by using a single medicine and only in high risk groups [74]. While in high-income countries, screening of pulmonary and lab staffs is recommended annually [75]. Also, based on the prevalence of LTBI in Iranian HCWs, it could be seen that Iranian HCWs training is not sufficient in confronting a patient with tuberculosis [25]. Hence, Iranian HCWs do not fully understand isolation and personal protection [25].

According to the results of meta-analysis, the lowest prevalence of LTBI in HCWs was in southern Iran (18.2%). The highest prevalence of LTBI in HCWs was reported in northern and western Iran. The high prevalence of LTBI in HCWs may be due to neighboring Azerbaijan and Iraq [76].

Azerbaijan which is listed on the high burden countries has high prevalence of multidrug resistance MTB [76-78]. In fact, the northern neighbors of Iran, such as Kazakhstan, Azerbaijan, are among the high burden countries with a high prevalence of multi-drug resistant tuberculosis [80].

On the other hands, the name of the country's western neighbor of Iran –Iraq- is not listed on the high burden countries [76-78] but according to reports from Ministry of Health - Iran Center for Medical Education and Treatment, Infectious Disease Control Center- the Iraqi

state may have become a high-risk source for tuberculosis after undergoing its recent crisis [79, 80].

The current study showed that 15.5% of the HCWs used before the BCG with at least a positive PPD test. According to studies, BCG does not protect adults from getting infected with tuberculosis, so the positive results of tuberculin testing in people vaccinated with BCG will be considered as a latent infection [81]. In other words, previous vaccination with BCG prevents tuberculin testing [82]. This may be due to a false positive reaction in PPD [25]. Some HCWs may respond to skin tests without being infected with mycobacterium [83]. The reason for these false-positive reactions may be due to contamination with non-tuberculosis mycobacterium, previous BCG, poor test performance or inappropriate interpretation of the test [83].

5. Limitations

Information about this meta-analysis was extracted from data published in Iranian databases as there was no access to the actual information of the control center of the Ministry of Health and Medical Education, so the exact prevalence of LTBI in HCWs could not be calculated.

Selection bias is able to limit the generalization of these findings because the type of bacteria strains in a country could be different with the other countries and could be related to descent diversities.

On the other hands, patients may not respond to skin test tuberculosis, even if they are infected with *Mycobacterium*. It may be due to skin allergies, recent infections (recent contact for 8 to 10 weeks), chronic infection, recent vaccinations with live viruses, advanced tuberculosis, some viral diseases (measles and bile), misdiagnosis skin or incorrect interpretation of the reaction. Patients may also respond to skin tests, even without being infected with *Mycobacterium*. The reason for these reactions may be due to contamination

with non-tuberculosis *Mycobacterium*, previous BCG, inappropriate test run or inappropriate interpretation of the test.

Despite the fact that the CDC updates the guidelines for the prevention and transmission of *M. tuberculosis* in health-care settings annually, the protocol for HCWs in Iran has not yet been prepared. Also, workshops could be developed to train tuberculosis prevention and self-care HCWs in the western regions of the Iran.

National databases are not sensitive to operators "AND" and "OR" to search for the combinations. Also, some databases were not fully accessible because of using Guilan University of Medical Sciences' - Iran Ministry of Health & Medical Education- VPN.

6. Conclusion

This meta-analysis showed the prevalence of LTBI in HCWs in Iran and estimated at 27.1%. The prevalence of LTBI in HCWs of Italy, Norway and India is reported to be equal to or less than HCWs of Iran. On the other hand, the highest prevalence of LTBI in HCWs in the north and the west of Iran may due to neighboring with Azerbaijan and Iraq which has become a high-risk source for tuberculosis by overcoming its recent years of crisis. Meanwhile, HCWs training is not sufficient in confronting a patient with tuberculosis, in Iran. Hence, Iranian HCWs do not fully understand the isolation and personal protection. We also found that BCG was not able to protect Iranian HCWs from TB infectious, completely.

7. Competing Interests

The authors declare that they have no competing interests.

8. Acknowledgment

We would like to thank the vice chancellor of research and technology, Guilan University of Medical Sciences (ID: IR.GUMS.REC.1397.513).

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11. Supporting information

S1 File. PRISMA Checklist

S2 File. The review protocol which has been registered in PROSPERO International Prospective Register of Systematic Reviews

S3 File. Newcastle-Ottawa scale checklist

S1 Table. Data characteristics (Full details) (MS Excel)

S1 Fig. The prevalence subgroup analysis (Forest plot - Random effect model) of TST/PPD induration diameter (48 hrs.) in HCWs with LTBI.

S2 Fig. The prevalence subgroup analysis (Forest plot - Random effect model) of TST/PPD induration diameter (48 hrs.) in HCWs with LTBI base on geographical region.

S3 Fig. Cumulative meta-analysis for overall prevalence of LTBI in HCWs.

S4 Fig. The prevalence subgroup analysis to employment duration (Forest plot - Random effect model) base on PPD (A), and QFT (B) in HCWs with LTBI.

S5 Fig. The prevalence subgroup analysis of gender (Forest plot - Random effect model) base on PPD (A), and QFT (B) in HCWs with LTBI.

S6 Fig. The prevalence subgroup analysis of age (Forest plot - Random effect model) base on PPD (A), and QFT (B) in HCWs with LTBI.

S7 Fig. The prevalence subgroup analysis of history TB contact (Forest plot - Random effect model) base on PPD (A), and QFT (B) in HCWs with LTBI.

S8 Fig. The prevalence subgroup analysis of TB clinical symptoms (Forest plot - Random effect model) base on PPD (A), and QFT (B) in HCWs with LTBI.

S9 Fig. The prevalence subgroup analysis of BCG (Forest plot - Random effect model) base on PPD (A), and QFT (B) in HCWs with LTBI.

S10 Fig. Publication bias of studies included due to the aim of prevalence of HCWs with LTBI.

12. Appendix: PubMed search strategy:

((Latent Tuberculosis) AND Iran AND Prevalence AND ((Health Personnel) OR (Healthcare Worker) OR (Health Care Provider))

Figure 1

Click here to access/download;Figure;Fig 1.JPG

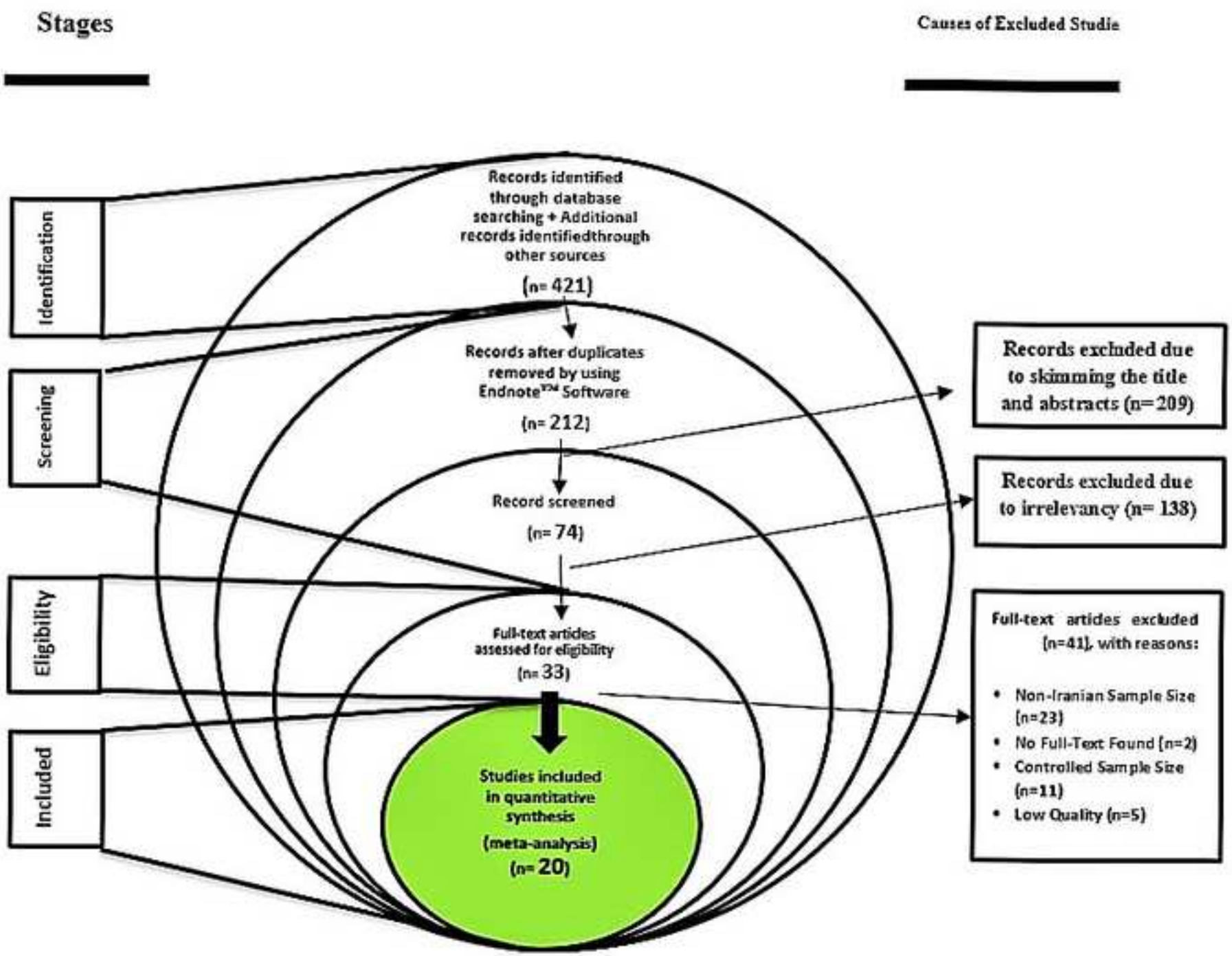
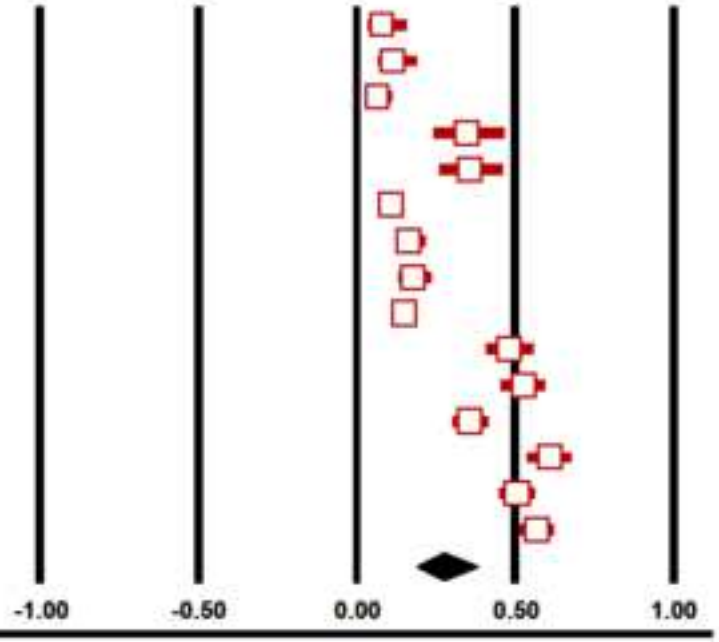


Figure 2

Click here to access/download;Figure;Fig 2.tif

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total	Relative weight
Taheri et al. (2013)	0.0787	0.0380	0.1559	-6.2494	0.0000	7 / 89	5.94
Davoodi et al., (2018)	0.1140	0.0674	0.1865	-6.9578	0.0000	13 / 114	6.36
Tavanaee Sani et al.(2015)	0.0650	0.0381	0.1087	-9.2953	0.0000	13 / 200	6.39
Vaziri et al., (2011)	0.3478	0.2453	0.4667	-2.4870	0.0129	24 / 69	6.51
Salmanzadeh et al.,(2016)	0.3563	0.2631	0.4619	-2.6416	0.0083	31 / 87	6.61
Alian et al., (2016)	0.1077	0.0772	0.1484	-11.2960	0.0000	32 / 297	6.72
Mostafavi et al., (2016)	0.1639	0.1226	0.2158	-9.4218	0.0000	40 / 244	6.76
nazer et al. (2015)	0.1794	0.1344	0.2353	-8.7120	0.0000	40 / 223	6.75
Ghafouri et al.,(2015)	0.1492	0.1199	0.1841	-13.5333	0.0000	71 / 476	6.86
Kariminia et al. (2009)	0.4830	0.4100	0.5566	-0.4522	0.6511	85 / 176	6.81
Talebi-Taher et al. (2011)	0.5250	0.4558	0.5933	0.7068	0.4797	105 / 200	6.83
SharafKhani et al. (2011)	0.3579	0.3055	0.4138	-4.8464	0.0000	107 / 299	6.87
Nikokar et al. (2010)	0.6108	0.5387	0.6784	2.9890	0.0028	113 / 185	6.81
Sayad et al. (2006)	0.5063	0.4515	0.5609	0.2243	0.8225	161 / 318	6.89
Salehi et al. (2016)	0.5671	0.5129	0.6197	2.4221	0.0154	186 / 328	6.89
	0.2713	0.1864	0.3770	-3.9872	0.0001		



Meta Analysis

Figure 3

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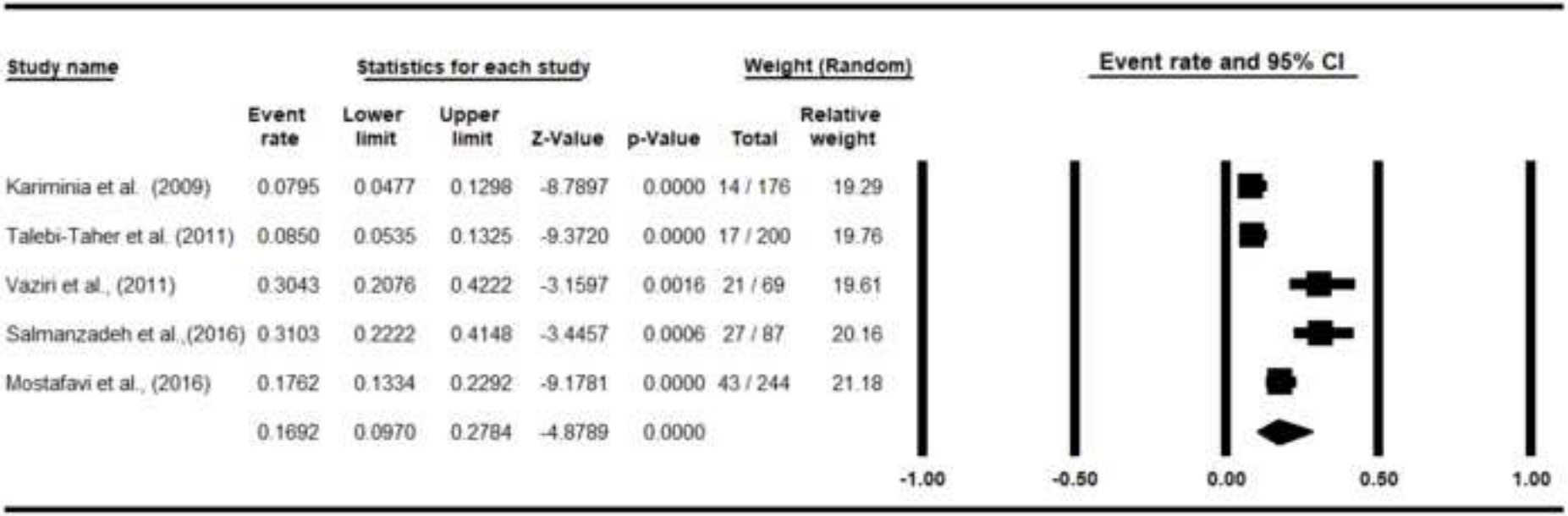

Meta Analysis

Figure 4

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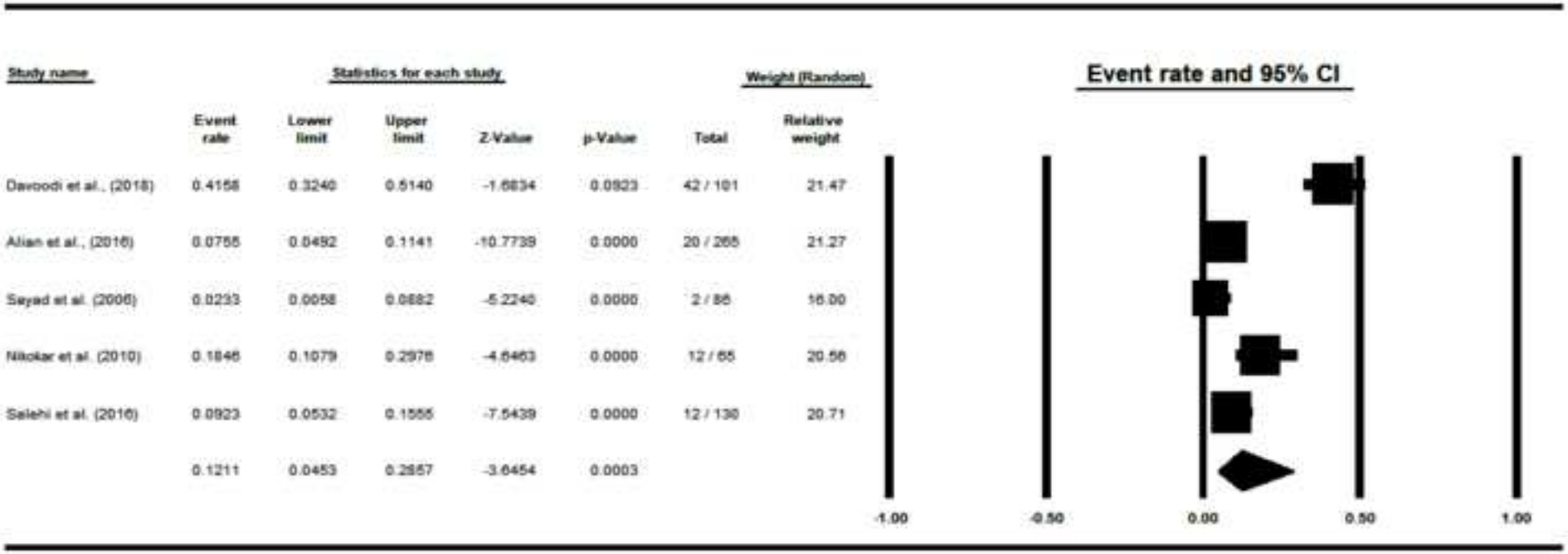

Meta Analysis

Figure 5

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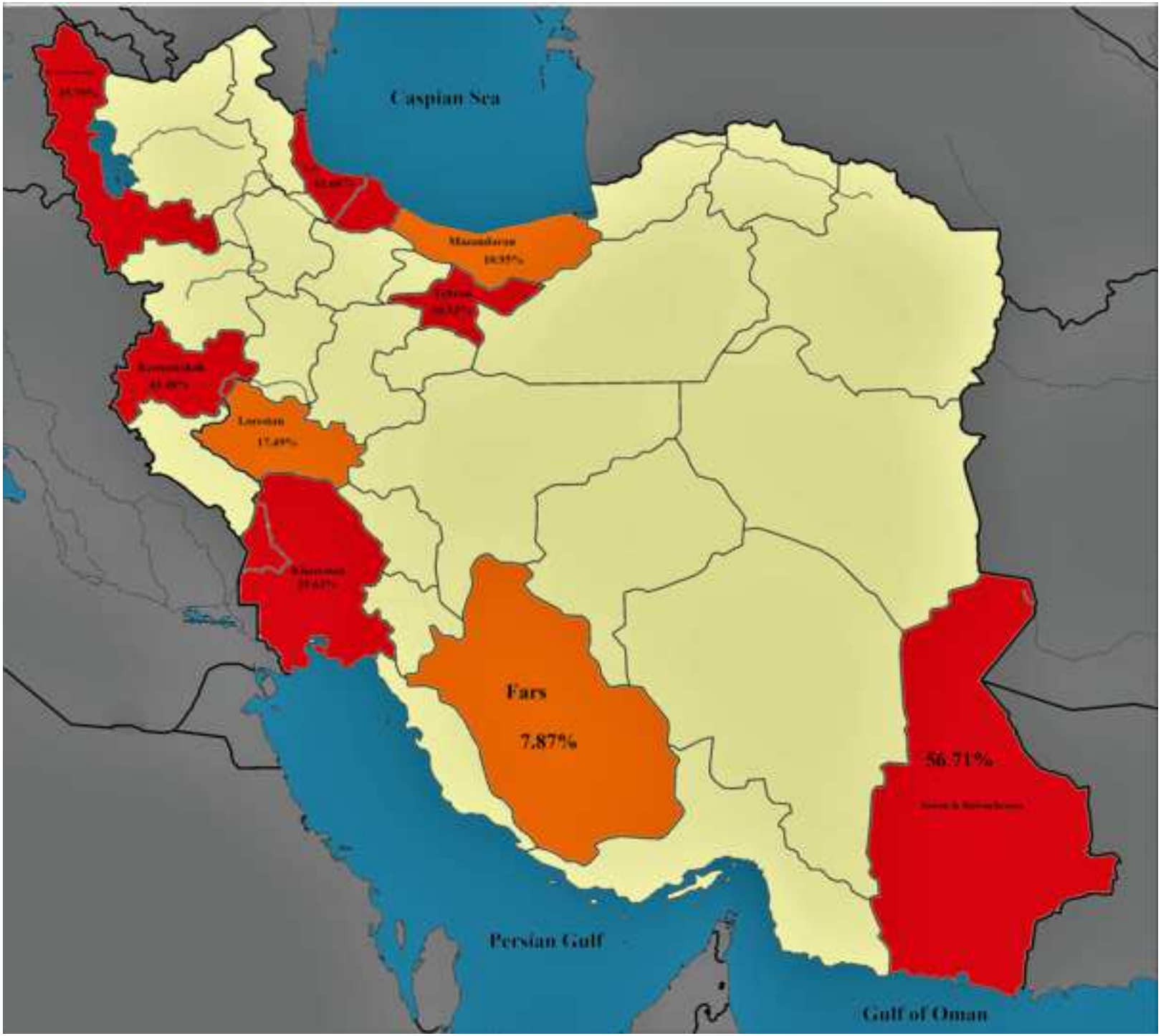

Figure 6

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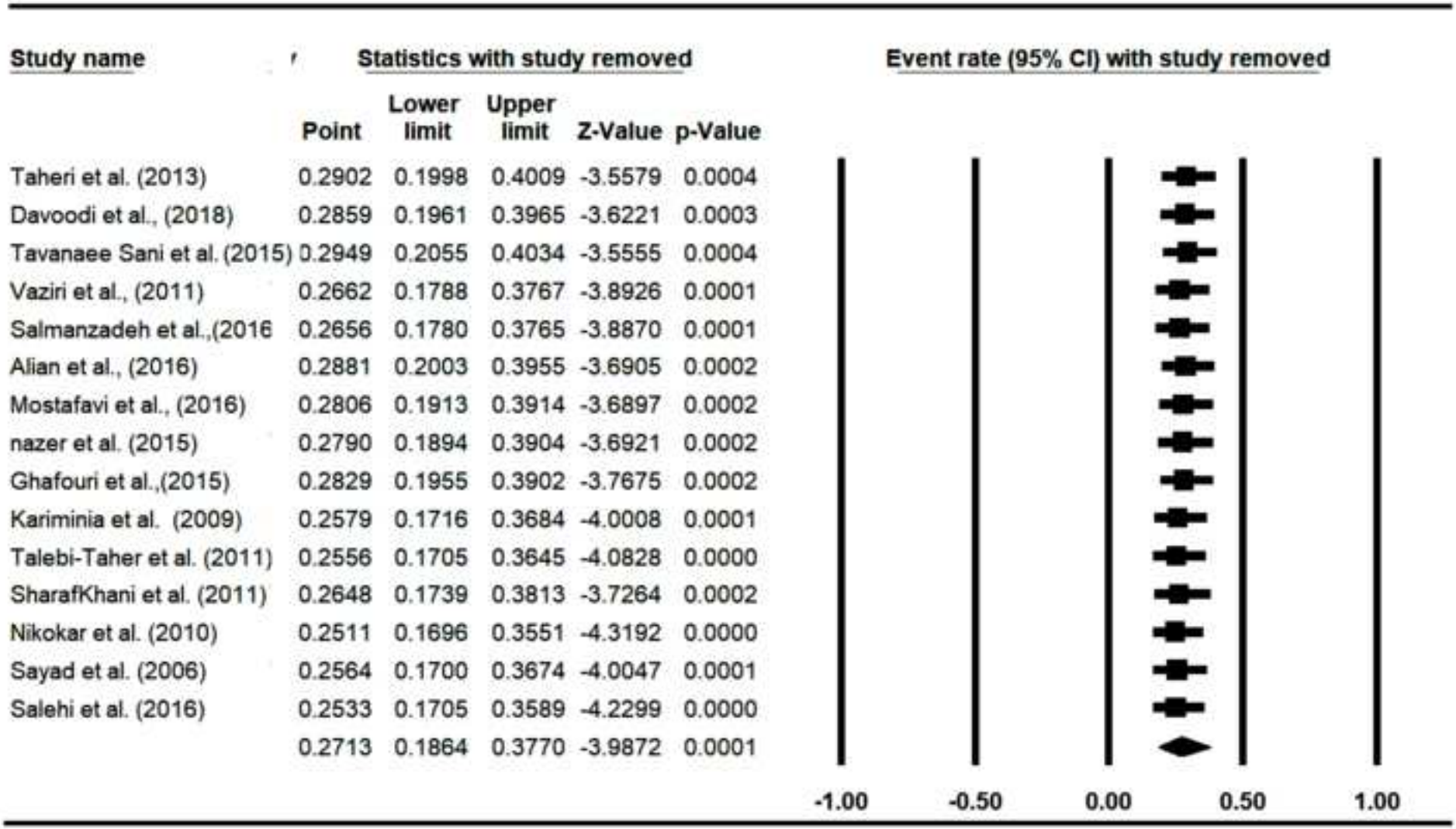

Meta Analysis

Figure 7

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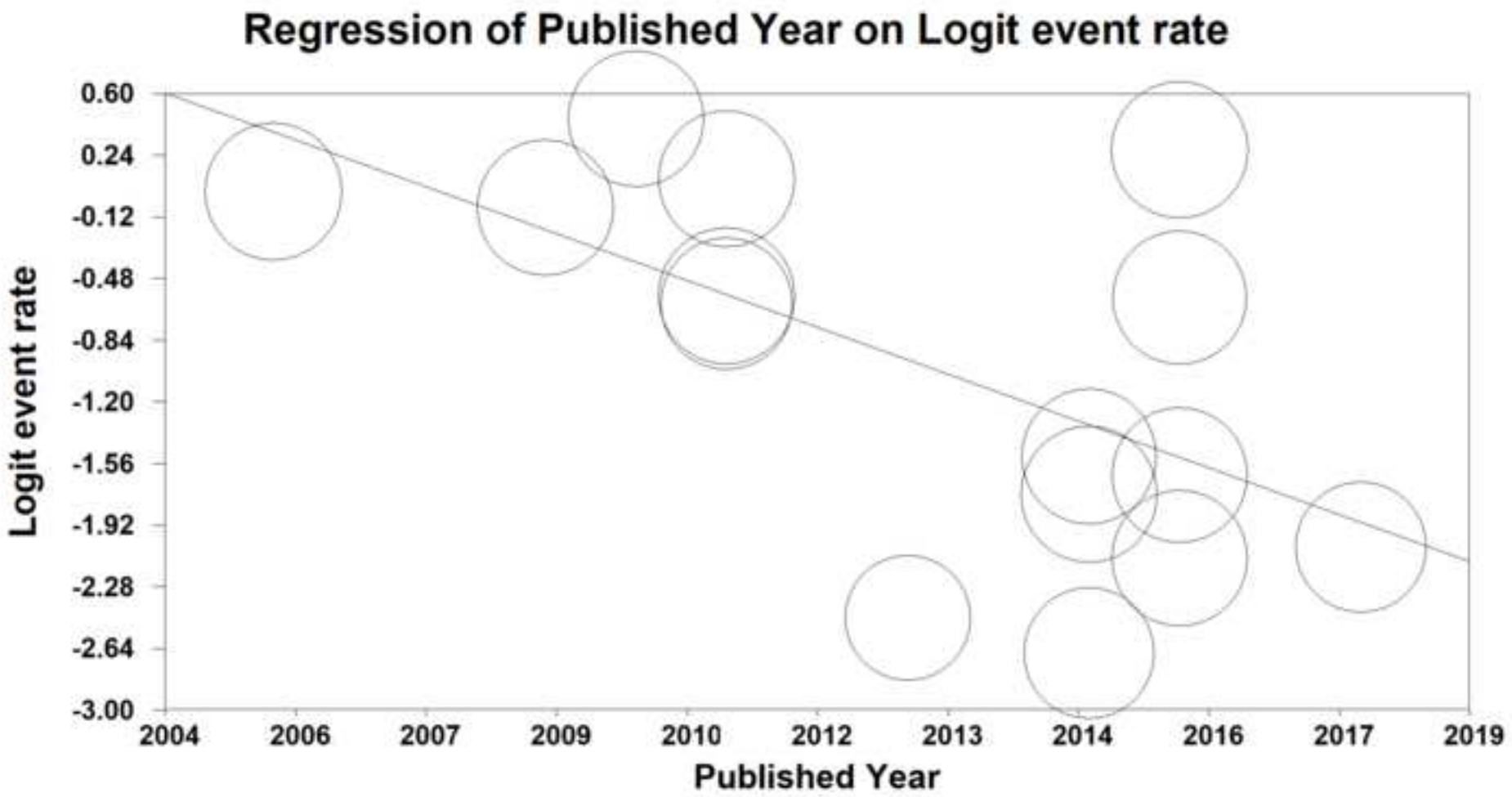

(Mixed effects regression (Method of moments); Slope = -0.1898(SE = 0.068, (95% CI: -0.323– -0.056)), Intercept = 381.14(SE = 137.43, (95% CI: 111.78–650.5)), P = 0.10653)

Figure 8

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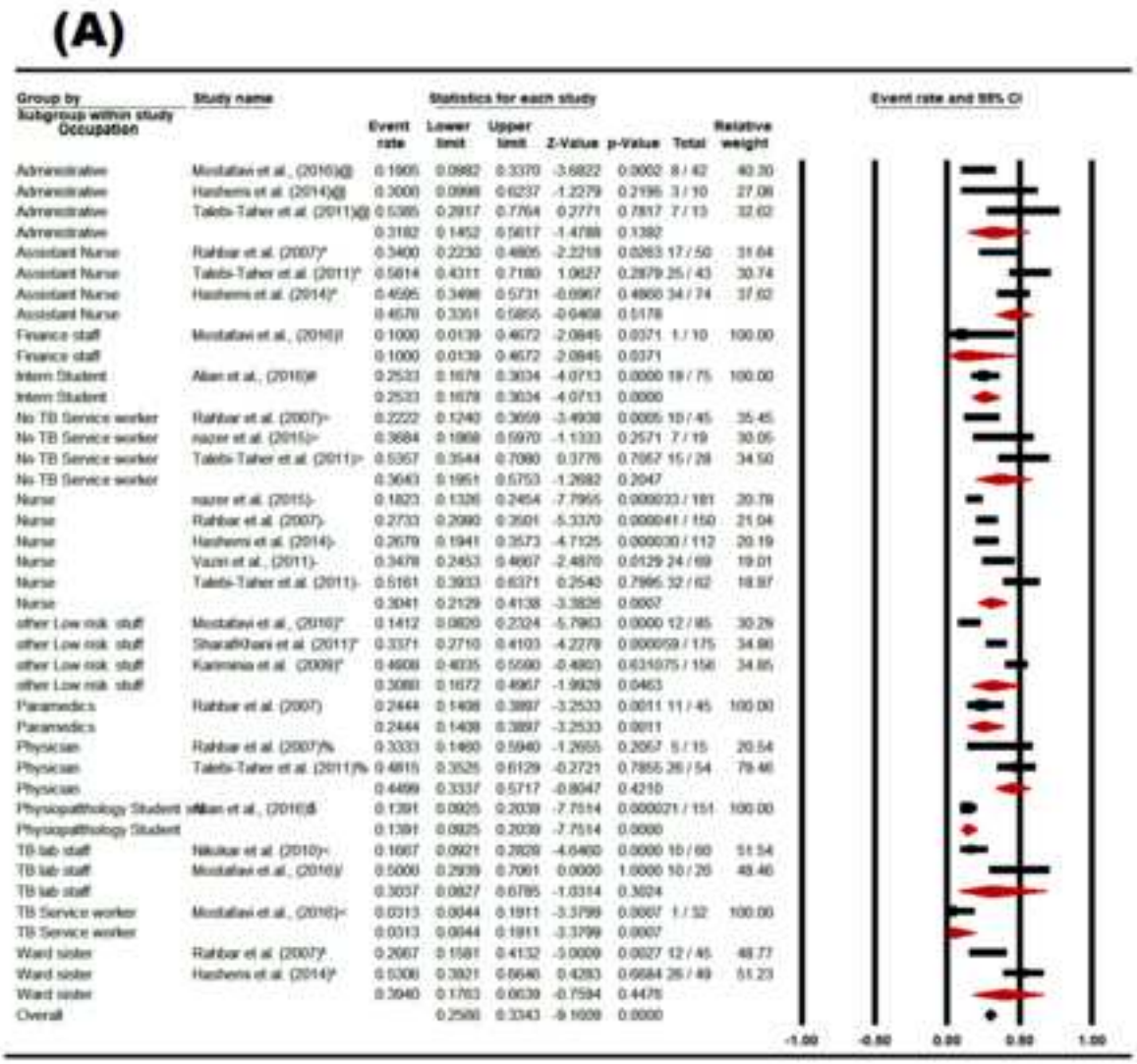

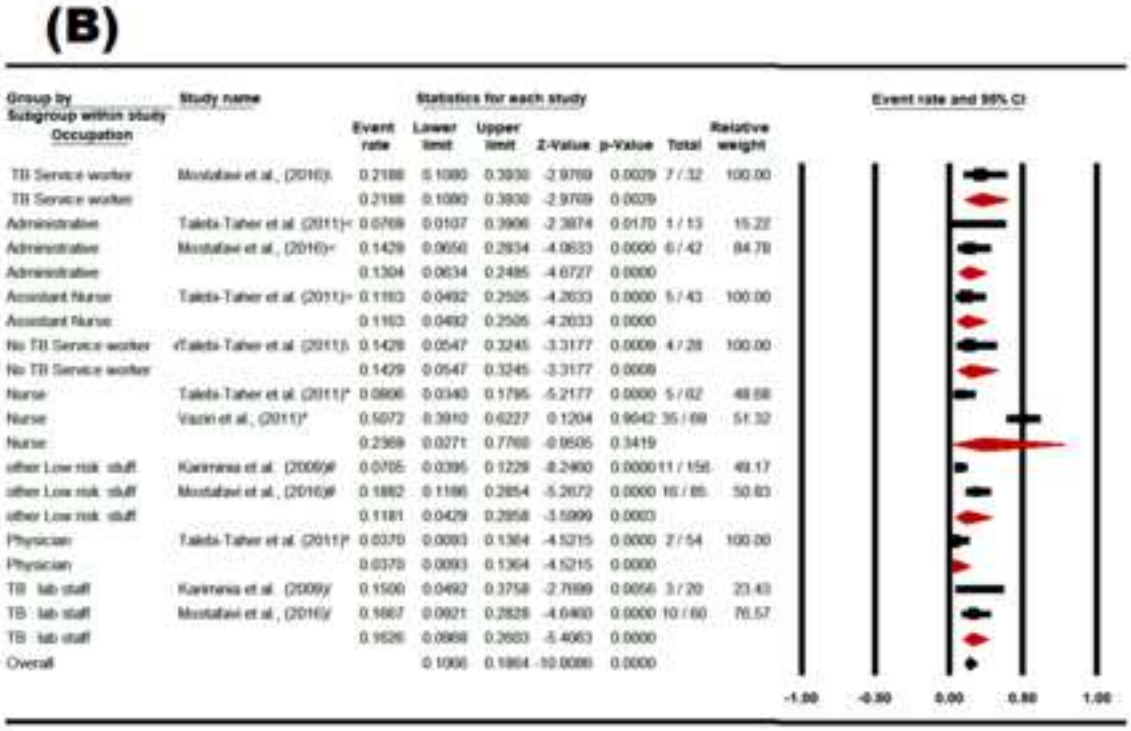

Figure 9

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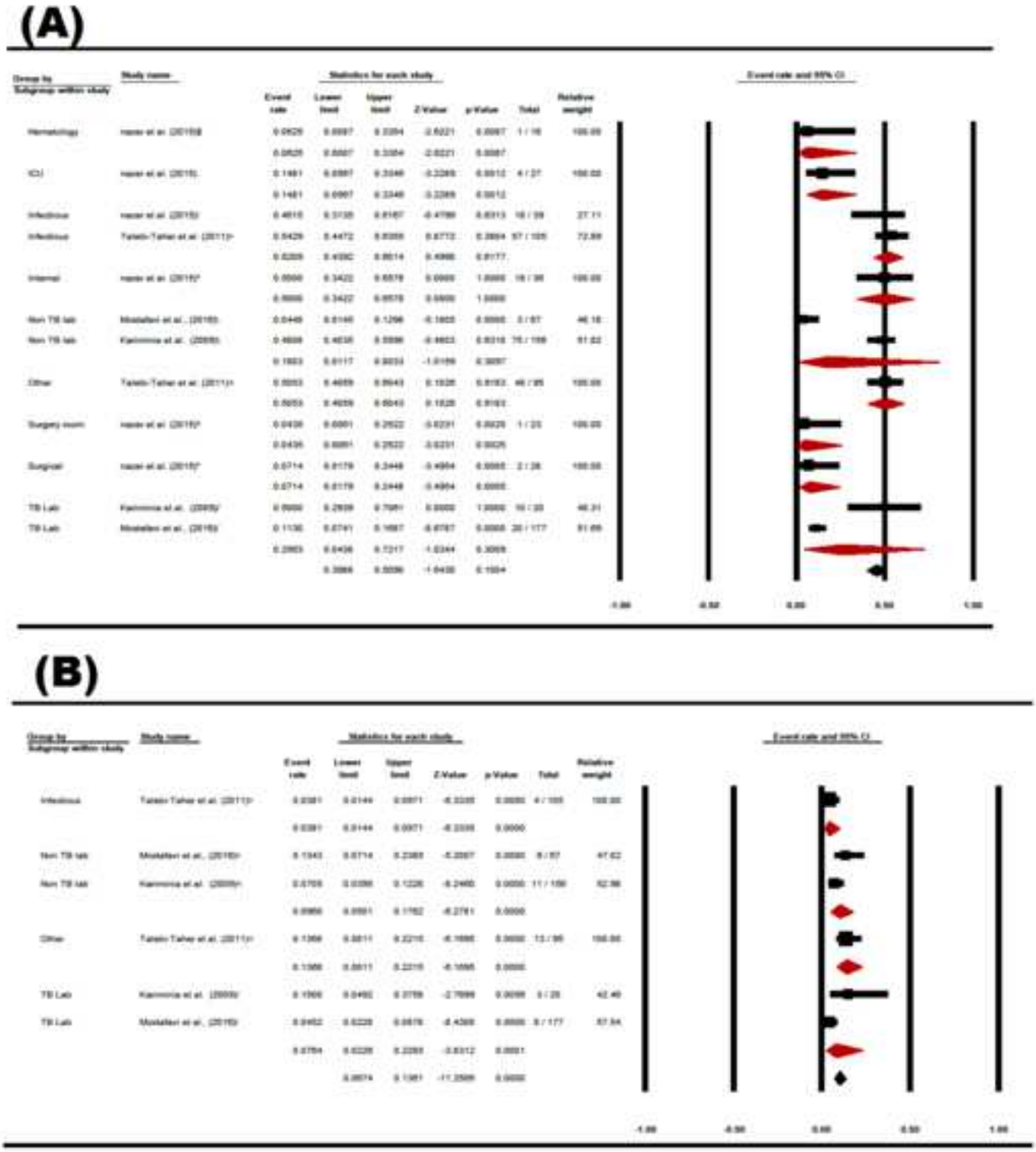

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