

# Epidemiology of Gastroesophageal Reflux Disease in Iran: A Systematic Review and Meta-analysis

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## Research article

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# Abstract

**Introduction :** Gastroesophageal reflux disease (GERD), which leads to acid reflux into the esophagus, is a common gastrointestinal disorder. Several studies have shown the prevalence of GERD in Iranian population, but their evidence is contradictory. Therefore, the present study was conducted to investigate the epidemiology of GERD in Iran.

**Methods:** The entire steps of this systematic review and meta-analysis were based on the MOOSE protocol, and the results were accordance with the PRISMA guideline. To find potentially relevant published articles, comprehensive search was done on international online databases Scopus, Science Direct, EMBASE, PubMed/Medline, CINAHL, EBSCO, Cochrane Library (Cochrane Database of Systematic Reviews - CDSR), Web of Science (ISI) and Iranian online databases IranDoc, (SID), Magiran, RICST, Iranian National Library, and Barakat Knowledge Network System and the Google Scholar search engine in June 2019. Cochran test and I<sup>2</sup> index were used to assess the heterogeneity of the studies. Data were analyzed using Comprehensive Meta-Analysis (CMA) software.

**Results:** The daily, weekly, monthly, and overall prevalence of GERD symptoms in Iranian population was 5.64% (95%CI [confidence interval]: 3.77%-8.35%; N=66,398), 12.50% (95%CI: 9.63%-16.08%; N=110,388), 18.62% (95%CI: 12.90%-26.12%; N= 70,749) and 43.07% (95%CI: 35.00%-51.53%; N=73,189), respectively. The daily, weekly, monthly, and overall prevalence of heartburn in Iranian population was 2.46% (95%CI: 0.93%-6.39%; N=18,774), 9.52% (95%CI: 6.16%-14.41%; N=54,125), 8.19% (95%CI: 2.42%-24.30%; N=19,363) and 23.20% (95%CI: 13.56%-36.79%; N=26,543), respectively. The daily, weekly, monthly, and overall prevalence of regurgitation in Iranian population was 4.00% (95%CI: 1.88%-8.32%; N=18,774), 9.79% (95%CI: 5.99%-15.60%; N=41,140), 13.76% (95%CI: 6.18%-44.31%; N=19,363) and 36.53% (95%CI: 19.30%-58.08%; N=21,174), respectively.

**Conclusion:** The present meta-analysis provides comprehensive and useful information on the epidemiology of GERD in Iran for policy-makers and health care providers. This study showed a high prevalence of GERD in Iran. Therefore, effective measures on GERD-related factors such as lifestyle can be among the health policies of Iran.

## 1. Background

Gastroesophageal reflux disease (GERD), which leads to acid reflux into the esophagus, is a common gastrointestinal disorder and results in typical painful symptoms such as heartburn and/or regurgitation (1). However, it may also appear with atypical symptoms including cough, asthma, chest pain, and fatigue (2).

Permanent acid reflux may cause more severe complications, including erosive esophagitis, esophageal strictures, Barrett's esophagus, esophageal adenocarcinoma, hiatus hernia, delayed gastric emptying, and visceral hypersensitivity (1, 3–5).

Several risk factors are associated with GERD, including Nonsteroidal Anti-inflammatory Drugs (NSAIDs), type of food, beverages, smoking, family history, high body mass index (BMI), physical activity, salt, or consuming pickles with meals and fast food, which are more associated with the lifestyle of the patient (5–7). It has also been shown that age, gender, pregnancy, and geographical variation are also related to GERD (7). In addition, it has been suggested that vertebral fractures and/or spinal malalignment may affect the incidence of GERD (8, 9).

A systematic review of longitudinal studies suggests that the incidence of GERD has increased in recent decades. If this trend continues, it may rapidly increase the serious complications of GERD, affect the patient's quality of life, and increase the cost of health care systems (10, 11).

Increasing the GERD awareness to improve Iranian people's health may be necessary. There is much information in Western cultures that can be generalized to an Iranian person but cannot match completely. Therefore, understanding the epidemiological effects of GERD in Iranian society can help healthcare professionals and policymakers take the next steps in creating the list of priorities for disease management.

Several studies have shown the prevalence of GERD in Iranian population, but their evidence is contradictory (12–46). Therefore, a structured review of all the documentation and their combination can provide a more complete picture of the dimensions of this disease in Iranian society. One of the main goals of meta-analysis, which is a combination of different studies, is to reduce the difference between parameters due to the increased number of studies involved in the analysis process. Another important goal of meta-analysis is to address inconsistencies in the results and their causes (42–45). Therefore, the present study was conducted to investigate the epidemiology of GERD in Iran.

## **2. Methods**

### **2.1 Study protocol**

The entire steps of this systematic review and meta-analysis were based on the Meta-analyses Of Observational Studies in Epidemiology) MOOSE) protocol (44), and the results were in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline (45). Two authors independently performed all study steps. In the case of dispute, a third author was involved.

### **2.2 Search strategy**

To find potentially relevant published articles, comprehensive search was done on international online databases Scopus, Science Direct, EMBASE, PubMed/Medline, CINAHL, EBSCO, Cochrane Library (Cochrane Database of Systematic Reviews - CDSR), Web of Science (ISI) and Iranian online databases Iranian Research Institute for Information Science and Technology (IranDoc ( (<https://irandoc.ac.ir>), Scientific Information Database (SID) (<http://www.sid.ir/>), Magiran (<http://www.magiran.com/>), Regional Information Center for Science and Technology (RICST) (<http://en.ricest.ac.ir/>), Iranian National Library

(<http://www.nlai.ir/>), and Barakat Knowledge Network System (<http://health.barakatkns.com>) and the Google Scholar search engine in June 2019. Our search was done to retrieve all literature related to GERD in Iran. The reference list of articles was reviewed to find the gray literature. The studies identified by our search strategies were entered into Endnote X7 (Thomson Reuters, Philadelphia, PA, USA) software.

The related articles were searched in PubMed using a combination of expressions and terms Medical Subject Heading (MeSH): "gastroesophageal reflux"[MeSH Terms] OR "gastroesophageal reflux disease" [Text Word] OR "heartburn"[MeSH Terms] AND "Iran"[Mesh]. Search terms were combined using Boolean operators of "OR" or "AND".

### **2.3 Study selection**

The two researchers independently reviewed the articles on the abovementioned databases. The third researcher examined the consistency between the data extracted by the two researchers, and the contradictory results were discussed and resolved. After collecting literature from the databases, the next step was to assess whether the articles corresponded to the content of the title and abstract. The second and third stages were the review of the remaining articles with full text.

### **2.4 Inclusion and exclusion criteria**

We included the studies that were: (1) written in English or Persian; (2) cross-sectional studies; (3) with the primary aim of reporting the prevalence of GERD, heartburn and regurgitation; and (4) performed among adults.

We excluded studies that: (1) had non-random sample size; (2) were non-relevant; (3) GERD diagnosis was not defined by heartburn and regurgitation; (4) were non-Iranian; (5) were case reports, review articles, congresses, letters to the editor without quantitative data, and theses.

### **2.5 Data extraction and management**

The two authors independently extracted the data. In case of duplicate publication, we considered the original report/article and, if necessary, additional details were extracted from the secondary articles.

For duplicate publications, we contacted the researchers to clarify the original publication, and if we did not get an answer, we chose the study with the largest number of participants for cases with overlapping data. We extracted the following data from each study: First author, year of publication, year of study, place of study, study design, method of diagnosis, data collection, characteristics of participants and estimation of prevalence.

### **2.6 Qualitative assessment**

The modified Scale of Newcastle Ottawa (NOS) was used to assess the quality of studies (46). The studies were divided into three categories based on the scores: high risk studies (scores ranging from 1 to

4), moderate risk (scores ranging from 5-7), and low risk (scores ranging from 8 to 10). Low and medium risk studies were included in the meta-analysis.

## 2.7 Statistical analysis

The prevalence of the disease is shown using the event rate. The 95% confidence intervals (CI) were calculated using Comprehensive Meta-Analysis (CMA) software using sample size (N) and standard error (SE). To determine women to men ratio, we calculated the odds ratio (OR). Cochran test and  $I^2$  index were used to assess the heterogeneity of the studies. There are three categories for  $I^2$  index:  $I^2$  index below 25% is low heterogeneity, 25-75% is medium, and above 75% is high heterogeneity (47, 48). For cases with low heterogeneity, the fixed effects model was used and for cases with medium and high heterogeneity, the random effects model was used. Subgroup analysis was used to find the cause of heterogeneity in the studies. Sensitivity analysis was performed by removing a study at a time to assess the predictive power. Mixed-effects meta-regression was used to investigate the relationship between continuous variables such as the time of study and the prevalence (49). Finally, distribution bias was evaluated using funnel plot, and Egger and Begg's tests. Statistical analysis and graph diagrams were performed using CMA version 2. The significance level of the test was considered to be  $P < 0.05$ .

## 3. Results

### 3.1 Search results and characteristics

Our initial search found 4260 records. After removing 2130 duplicates, 2130 unique documents were reviewed for relating the titles and abstract. Then, we reviewed the full text of 350 articles. Finally, 30 articles (23 studies for GERD, 20 studies for heartburn, and 13 studies for regurgitation) were included in the study (Figure 1). The mean age of the participants (in 14 reported studies) was 39.35 years (95% CI: 34.98-43.71). Table 1 shows the characteristics of each study.

### 3.2 GERD prevalence and sensitivity analysis

The daily, weekly, monthly, and overall prevalence of GERD symptoms in Iranian population was 5.64% (95% CI: 3.77%-8.35%; heterogeneity:  $I^2 = 98.76%$ ,  $P < 0.001$ ;  $N = 66,398$ ), 12.50% (95% CI: 9.63%-16.08%; heterogeneity:  $I^2 = 99.50%$ ,  $P < 0.001$ ;  $N = 110,388$ ), 18.62% (95% CI: 12.90%-26.12%; heterogeneity:  $I^2 = 99.66%$ ,  $P < 0.001$ ;  $N = 70,749$ ) and 43.07% (95% CI: 35.00%-51.53%; heterogeneity:  $I^2 = 99.66%$ ,  $P < 0.001$ ;  $N = 73,189$ ), respectively (Figure 2).

The sensitivity analysis for prevalence of all types GERD symptoms by removing a study showed that the overall result is still powerful (Figure 1-Supplement).

### 3.3 Subgroup analysis of GERD

The subgroup analysis for the daily, weekly, monthly, and overall prevalence of GERD symptoms is shown in Table 2. For the daily prevalence of GERD, the subgroup analysis of the study population ( $P < 0.001$ ) and the data collection method ( $P = 0.019$ ) were significant. For the weekly prevalence of GERD, subgroup analysis of the area ( $P = 0.001$ ) and study population ( $P < 0.001$ ) were significant. For the monthly prevalence of GERD, the subgroup analysis of the population was significant ( $P = 0.001$ ). For the overall prevalence of GERD, the subgroup analysis of the area ( $P < 0.001$ ), the study population ( $P < 0.001$ ) and the quality of studies ( $P = 0.005$ ) were significant. Other variables were not significant.

### 3.4 The prevalence of GERD by gender

The daily, weekly, monthly, and overall prevalence of GERD symptoms in Iranian males was 5.72% (95% CI: 3.41%-9.46%; heterogeneity:  $I^2 = 97.44\%$ ,  $P < 0.001$ ;  $N = 26,004$ ), 11.38% (95% CI: 6.69%-12.01%; heterogeneity:  $I^2 = 97.80\%$ ,  $P < 0.001$ ;  $N = 19,453$ ), 15.68% (95% CI: 10.67%-22.45%; heterogeneity:  $I^2 = 98.15\%$ ,  $P < 0.001$ ;  $N = 8,865$ ) and 39.26% (95% CI: 32.35%-46.62%; heterogeneity:  $I^2 = 99.04\%$ ,  $P < 0.001$ ;  $N = 31,704$ ) (Figure 2-supplementary).

The daily, weekly, monthly, and overall prevalence of GERD symptoms in Iranian females was 7.88% (95% CI: 3.67%-16.11%; heterogeneity:  $I^2 = 98.56\%$ ,  $P < 0.001$ ;  $N = 31,588$ ), 12.81% (95% CI: 9.47%-17.10%; heterogeneity:  $I^2 = 98.04\%$ ,  $P < 0.001$ ;  $N = 19,380$ ), 16.96% (95% CI: 13.17%-21.56%; heterogeneity:  $I^2 = 98.17\%$ ,  $P < 0.001$ ;  $N = 21,567$ ), 17.07% (95% CI: 13.20%-21.56%; heterogeneity:  $I^2 = 96.26\%$ ,  $P < 0.001$ ;  $N = 8,563$ ), and 45.51% (95% CI: 38.22%-52.99%; heterogeneity:  $I^2 = 98.99\%$ ,  $P < 0.001$ ;  $N = 38,252$ ) (Figure 3-supplementary).

Odds ratio (OR) for the prevalence of daily, weekly, monthly, and overall prevalence of GERD in women compared to men in Table 2 shows that there is a significant difference only in the daily prevalence of GERD ( $P = 0.003$ ).

### 3.5 Meta-regression and publication bias for prevalence of GERD

The meta-regression model based on years of study for GERD prevalence revealed that the meta-regression coefficient for daily, weekly, monthly, and overall prevalence of GERD was (-0.022, 95% CI -0.132 to 0.087,  $P = 0.688$ ), (0.025, 95% CI -0.410 to 0.092,  $P = 0.450$ ), (0.0140, 95% CI -0.057 to 0.085,  $P = 0.700$ ) and (0.038, 95% CI -0.081 to 0.085,  $P = 0.104$ ), respectively (Figure 3).

Regarding publication bias, the significance level of Egger and Begg's tests was (Egger=0.024 and Begg's=0.152), (Egger=0.628 and Begg's=0.624), (Egger< 0.001 and Begg's=0.533) and (Egger=0.002 and Begg's=0.754) for the daily, weekly, monthly, and overall prevalence of GERD, respectively (Figure 4-supplementary).

### 3.6 Heartburn prevalence and sensitivity analysis

The daily, weekly, monthly, and overall prevalence of heartburn in Iranian population was 2.46% (95% CI: 0.93%-6.39%; heterogeneity:  $I^2= 99.15\%$ ,  $P< 0.001$ ;  $N= 18,774$ ), 9.52% (95% CI: 6.16%-14.41%; heterogeneity:  $I^2= 99.58\%$ ,  $P< 0.001$ ;  $N= 54,125$ ), 8.19% (95% CI: 2.42%-24.30%; heterogeneity:  $I^2= 99.76\%$ ,  $P< 0.001$ ;  $N= 19,363$ ) and 23.20% (95% CI: 13.56%-36.79%; heterogeneity:  $I^2= 99.77\%$ ,  $P< 0.001$ ;  $N= 26,543$ ), respectively (Figure 4).

The sensitivity analysis for prevalence of daily, weekly, monthly, and overall prevalence of heartburn by removing a study showed that the overall result is still powerful (Figure 5-Supplement).

### 3.7 Subgroup analysis of heartburn

For the daily prevalence of heartburn, the subgroup analysis of the area ( $P< 0.001$ ), study population ( $P< 0.001$ ) and the quality of studies ( $P< 0.001$ ) were significant. For the weekly prevalence of heartburn, subgroup analysis of the area ( $P = 0.001$ ), study population ( $P< 0.001$ ) and year of study ( $P= 0.021$ ) were significant. For the monthly prevalence of heartburn, the subgroup analysis of the population was significant ( $P = 0.044$ ). For the overall prevalence of heartburn, the subgroup analysis of the area ( $P= 0.019$ ), and the study population ( $P< 0.001$ ) were significant. Other variables were not significant.

### 3.8 The prevalence of heartburn by gender

The daily, weekly, monthly, and overall prevalence of heartburn in Iranian males was .61% (95% CI: 0.59%-10.75%; heterogeneity:  $I^2= 98.19\%$ ,  $P< 0.001$ ;  $N= 4,778$ ), 5.68% (95% CI: 1.81%-16.44%; heterogeneity:  $I^2= 98.69\%$ ,  $P< 0.001$ ;  $N= 7,257$ ), 5.93% (95% CI: 3.93%-8.84%; heterogeneity:  $I^2= 89.65\%$ ,  $P< 0.001$ ;  $N= 4,788$ ) and 16.54% (95% CI: 10.9%-24.28%; heterogeneity:  $I^2= 96.43\%$ ,  $P< 0.001$ ;  $N= 1,788$ ) (Figure 6-supplementary).

The daily, weekly, monthly, and overall prevalence of heartburn in Iranian females was 2.90% (95% CI: 0.36%-19.95%; heterogeneity:  $I^2= 98.45\%$ ,  $P< 0.001$ ;  $N= 2,803$ ), 6.89% (95% CI: 2.96%-15.21%; heterogeneity:  $I^2= 98.02\%$ ,  $P< 0.001$ ;  $N= 5,171$ ), 9.90% (95% CI: 6.45%-14.90%; heterogeneity:  $I^2= 92.19\%$ ,  $P< 0.001$ ;  $N= 3,183$ ), 22.28% (95% CI: 12.31%-36.91%; heterogeneity:  $I^2= 98.02\%$ ,  $P< 0.001$ ;  $N= 2,803$ ) (Figure 7-supplementary).

OR for the prevalence of daily, weekly, monthly, and overall prevalence of heartburn in women compared to men in Table 2 shows that there is a significant difference in the weekly ( $P= 0.015$ ), monthly ( $P< 0.001$ ) and overall ( $P = 0.008$ ) prevalence of heartburn.

### 3.9 Meta-regression and publication bias for prevalence of heartburn

The meta-regression model based on years of study for heartburn prevalence revealed that the meta-regression coefficient for daily, weekly, monthly, and overall prevalence of heartburn was (0.136, 95% CI -0.241 to 0.514,  $P = 0.478$ ), (0.109, 95% CI 0.013 to 0.205,  $P = 0.025$ ), (0.205, 95% CI 0.004 to 0.405,  $P=0.044$ ) and (0.047, 95% CI -0.103 to 0.198,  $P = 0.539$ ), respectively (Figure 5).

Regarding publication bias, the significance level of Egger and Begg's tests was (Egger=0.028 and Begg's=0.707), (Egger=0.118 and Begg's=0.392), (Egger=0.005 and Begg's=0.548) and (Egger=0.025 and Begg's=0.754) for the daily, weekly, monthly, and overall prevalence of heartburn, respectively (Figure 8-supplementary).

### 3.10 Regurgitation prevalence and sensitivity analysis

The daily, weekly, monthly, and overall prevalence of regurgitation in Iranian population was 4.00% (95% CI: 1.88%-8.32%; heterogeneity:  $I^2= 99.03\%$ ,  $P < 0.001$ ;  $N= 18,774$ ), 9.79% (95% CI: 5.99%-15.60%; heterogeneity:  $I^2= 99.55\%$ ,  $P < 0.001$ ;  $N= 41,140$ ), 13.76% (95% CI: 6.18%-44.31%; heterogeneity:  $I^2= 99.73\%$ ,  $P < 0.001$ ;  $N= 19,363$ ) and 36.53% (95% CI: 19.30%-58.08%; heterogeneity:  $I^2= 99.86\%$ ,  $P < 0.001$ ;  $N= 21,174$ ), respectively (Figure 6).

The sensitivity analysis for prevalence of all types regurgitation symptoms by removing a study showed that the overall result is still powerful (Figure 9-Supplement).

### 3.11 Subgroup analysis of regurgitation

For the daily prevalence of regurgitation, the subgroup analysis of the area ( $P < 0.001$ ), study population ( $P < 0.001$ ), the quality of studies ( $P < 0.001$ ) and the data collection method ( $P = 0.019$ ) were significant. For the weekly prevalence of regurgitation, subgroup analysis of the area ( $P = 0.001$ ) was significant. For the monthly regurgitation of heartburn, the subgroup analysis of the population was significant ( $P < 0.001$ ). For the overall prevalence of regurgitation, the subgroup analysis of the area ( $P = 0.019$ ), and the study population ( $P = 0.019$ ) were significant. Other variables were not significant.

### 3.12 The prevalence of regurgitation by gender

The daily, weekly, monthly, and overall prevalence of regurgitation in Iranian males was 3.59% (95% CI: 1.17%-10.47%; heterogeneity:  $I^2= 97.58\%$ ,  $P < 0.001$ ;  $N= 4,788$ ), 7.93% (95% CI: 4.55%-13.46%; heterogeneity:  $I^2= 95.25\%$ ,  $P < 0.001$ ;  $N= 5,008$ ), 10.15% (95% CI: 5.61%-17.70%; heterogeneity:  $I^2= 97.28\%$ ,  $P < 0.001$ ;  $N= 4,788$ ) and 28.00% (95% CI: 24.66%-31.60%; heterogeneity:  $I^2= 81.76\%$ ,  $P < 0.001$ ;  $N= 4,788$ ) (Figure 10-supplementary).

The daily, weekly, monthly, and overall prevalence of regurgitation in Iranian females was 4.63% (95% CI: 0.78%-23.11%; heterogeneity:  $I^2= 98.76\%$ ,  $P < 0.001$ ;  $N= 2,803$ ), 6.81% (95% CI: 3.64%-12.41%; heterogeneity:  $I^2= 94.86\%$ ,  $P < 0.001$ ;  $N= 3,183$ ), 5.23% (95% CI: 1.11%-21.34%; heterogeneity:  $I^2= 98.49\%$ ,  $P < 0.001$ ;  $N= 2,803$ ) and 30.59% (95% CI: 17.89%-47.14%; heterogeneity:  $I^2= 98.29\%$ ,  $P < 0.001$ ;  $N= 2,803$ ) (Figure 11-supplementary).

OR for the prevalence of daily, weekly, monthly, and overall prevalence of regurgitation in women compared to men in Table 2 shows that there is no significant difference in the prevalence of regurgitation.

### 3.13 Meta-regression and publication bias for prevalence of regurgitation

The meta-regression model based on years of study for heartburn prevalence revealed that the meta-regression coefficient for daily, weekly, monthly, and overall prevalence of heartburn was (0.091, 95% CI -0.206 to 0.390,  $P = 0.546$ ), (0.081, 95% CI -0.029 to 0.192,  $P = 0.149$ ), (0.162, 95% CI 0.027 to 0.297,  $P=0.018$ ) and (0.193, 95% CI 0.062 to 0.072,  $P = 0.001$ ), respectively (Figure 7).

Regarding publication bias, the significance level of Egger and Begg's tests was (Egger=0.060 and Begg's=0.452), (Egger=0.221 and Begg's=0.999), (Egger=0.011 and Begg's=0.999) and (Egger=0.074 and Begg's=0.763) for the daily, weekly, monthly, and overall prevalence of heartburn, respectively (Figure 12-supplementary).

## 4. Discussion

The present study is the first systematic review and meta-analysis on the prevalence of GERD in Iran. In this study, the prevalence of daily, weekly, monthly, and overall prevalence of GERD in Iranian population was 5.64%, 12.50%, 18.62%, and 43.07%, respectively. In a systematic review in 2014, the weekly prevalence of GERD in North America was 18.1–27.8%, in South America was 23.0%, in Europe was 8.8–25.9%, in East Asia was 2.5–7.8%, in Middle East was 8.7–33.1% and in Australia was 11.6%, and was specifically reported for Iran to be 10.1–15.0% (50), which is consistent with the present study.

In the present study, the causes of heterogeneity in the studies can be attributed to the geographic region and the studied population, while previous studies also mentioned racial and geographical factors for the pathogenesis of GERD (50, 51).

In a systematic review in Iran, the causes of heterogeneity for the prevalence of GERD have been attributed to different criteria such as definition, difference in social factors, cultural background, and lifestyle in different cities or different populations (52). On the other hand, due to the limitations of population-based studies, where precise diagnostic methods such as PH metric testing cannot be used, some of these differences can be due to the lack of a comprehensive standard for classifying symptoms and complications of GERD, which makes comparison between studies difficult (53). Some differences in reported reflux rates may be due to cultural and ethnic differences in perceiving, expressing, and understanding symptoms of reflux. For example, there are differences in describing symptoms and diseases in some areas and among some ethnic groups, while other groups do not pay attention to the symptoms of the disease. It has been pointed out that different groups and cultures have different perceptions of the word "heartburn". In a study in Boston among different ethnic groups, only 13% of Chinese and Korean people had a proper understanding of the word "heartburn" (54).

Iranian people are gaining weight such that the prevalence of obesity in Iranian adults is 21.5% (55). Meanwhile, the economic and social status of people has changed rapidly. Therefore, some studies have

reported that the above factors are important risk factors (56).

Smoking has always been associated with GERD. The relationship between smoking and GERD (any symptoms) continues even after smoking is stopped (41). Smoking increases the frequency of gastroesophageal reflux by reducing the pressure of the sphincter (57) and decreases the secretion of the bicarbonate of the saliva (58). However, some other mechanisms may also be involved in the relationship between smoking and symptoms of GERD. Therefore, smoking may result in exaggerated negative intrathoracic pressure and inspiratory thoraco-abdominal pressure gradient, which may cause gastrointestinal reflux (59, 60). In a meta-analysis, the prevalence of smoking among Iranian men and women was reported to be 21.7% and 3.6%, respectively (60).

There is varied evidence regarding the relationship between gender and GERD symptoms, but most studies show no relationship (61). However, in many studies based on endoscopy, non-erosive and erosive GERD are more common in men and women, respectively (62, 63). In the present study, only the daily symptoms of GERD were significantly higher in women compared to men.

The prevalence of GERD-related symptoms and tissue damage is different in ethnic/racial groups (64, 65). We found a significant difference between the weekly and overall prevalence of GERD in different areas; the weekly and overall prevalence of GERD in the south was 21.26% and in the north was 60.86%. Iran has different ethnicities (Kurds, Persians, Turks, Arabs, Turkmen, etc.) with different customs and lifestyles, each of which predominantly lives in certain geographic area (e.g., Kurds are concentrated in western Iran) (66). Nevertheless, the environmental or genetic factors that affect these differences are not clear yet (41).

The study with highest quality in this meta-analysis was the study of Islami et al. (41) on 49975 people of the general population, with a daily, weekly, monthly, and overall GERD prevalence of 11.83%, 8.06%, 40.96%, and 60.86%, respectively, who reported a high incidence.

In the present study, the prevalence of daily, weekly, monthly, and overall prevalence of GERD did not change significantly over time. In 2005, a systematic review on population-based studies reported the weekly prevalence of GERD to be 10–20% in Europe and the United States and less than 5% in East Asia (67). However, in a more recent systematic review in 2011, the weekly prevalence of GERD was reported to be 8.8–25.9% in Europe and 18.1–27.8% in North America and 2.5–7.8% in East Asia (50). Therefore, the global prevalence of GERD is increasing over time (50).

There were several limitations for this early study, so interpreting the results should be done with cautious. The questionnaire consisted of only the major and common symptoms of GERD such as heartburn and acid reflux, but not other symptoms. Non-gastric manifestations of GERD are not included. Indeed, in the absence of a golden standard for the diagnosis of GERD, we only have the questionnaires, which are common in clinical or epidemiological studies.

## 5. Conclusion

The present meta-analysis provides comprehensive and useful information on the epidemiology of GERD in Iran for policy-makers and health care providers. This study showed a high prevalence of GERD in Iran. Therefore, effective measures on GERD-related factors such as lifestyle can be among the health policies of Iran.

## Abbreviations

GERD Gastroesophageal reflux disease

NSAIDs Nonsteroidal Anti-inflammatory Drugs

BMI Body mass index

IranDoc Iranian Research Institute for Information Science and Technology

SID Scientific Information Database

RICST Regional Information Center for Science and Technology  
MOOSE Meta-analyses Of Observational Studies in Epidemiology

PRISMA Systematic Reviews and Meta-analysis

OR Odds ratio

CI Confidence interval

## Declarations

### **Ethics approval and consent to participate**

Not applicable.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

Not applicable.

### **Competing interests**

There is not conflict of interest between the authors of this study.

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### **Authors' contributions**

MA, MS, and MK acquired the data. MA and MK analyzed and interpreted the data. MA drafted the manuscript; MA, MS, and MK critically revised the manuscript for important intellectual content. MK supervised the study.

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## Tables

Not available with this version of the manuscript.

## Supplementary Files

Figure 1- supplementary: The sensitivity analysis for daily (A), weekly (B), monthly (C), and overall (D) prevalence of GERD symptoms in Iranian population

Figure 2-supplementary: The daily (A), weekly (B), monthly (C), and overall (D) prevalence of GERD symptoms in Iranian males

Figure 3-supplementary: The daily (A), weekly (B), monthly (C), and overall (D) prevalence of GERD symptoms in Iranian females

Figure 4-supplementary: Publication bias for daily (A), weekly (B), monthly (C), and overall (D) prevalence of GERD symptoms

Figure 5- supplementary: The sensitivity analysis for daily (A), weekly (B), monthly (C), and overall (D) prevalence of heartburn in Iranian population

Figure 6-supplementary: The daily (A), weekly (B), monthly (C), and overall (D) prevalence of heartburn in Iranian males

Figure 7-supplementary: The daily (A), weekly (B), monthly (C), and overall (D) prevalence of heartburn in Iranian females

Figure 8-supplementary: Publication bias for daily (A), weekly (B), monthly (C), and overall (D) prevalence of heartburn

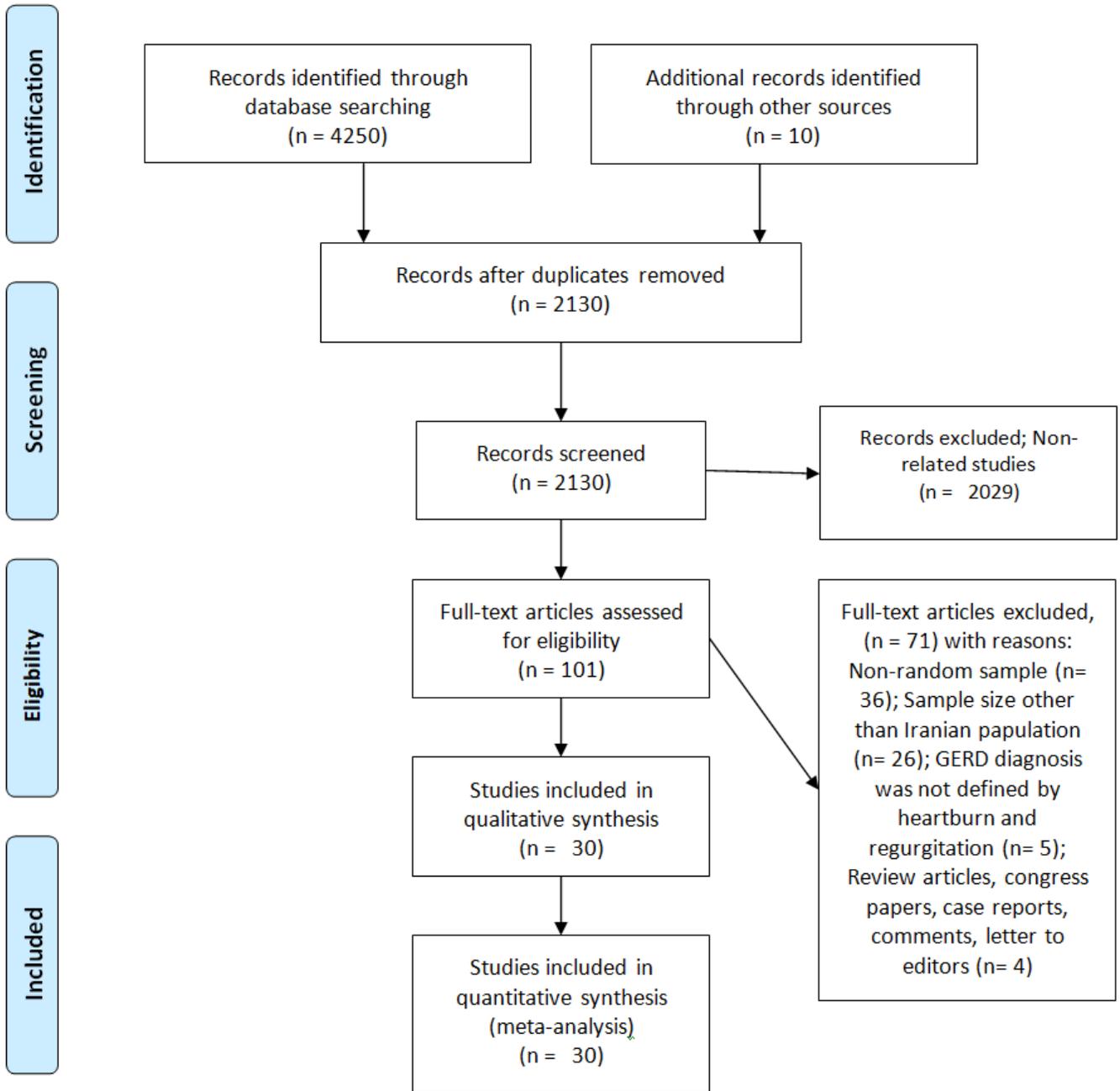
Figure 9- supplementary: The sensitivity analysis for daily (A), weekly (B), monthly (C), and overall (D) prevalence of regurgitation in Iranian population

Figure 10-supplementary: The daily (A), weekly (B), monthly (C), and overall (D) prevalence of regurgitation in Iranian males

Figure 11-supplementary: The daily (A), weekly (B), monthly (C), and overall (D) prevalence of regurgitation in Iranian females

Figure 12-supplementary: Publication bias for daily (A), weekly (B), monthly (C), and overall (D) prevalence of regurgitation

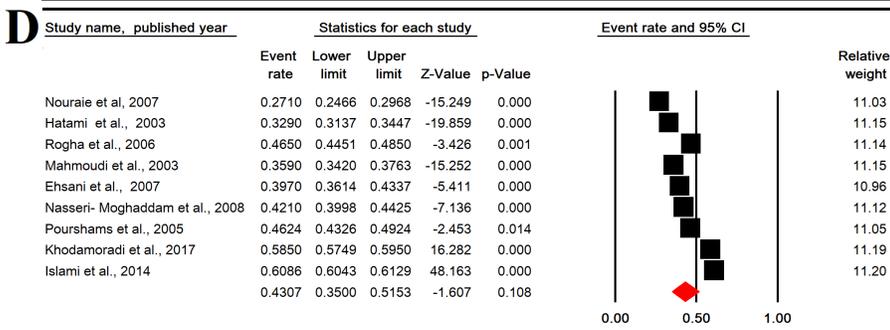
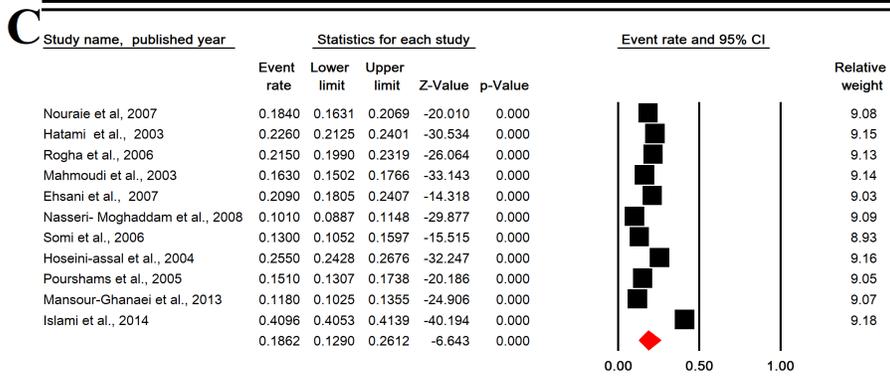
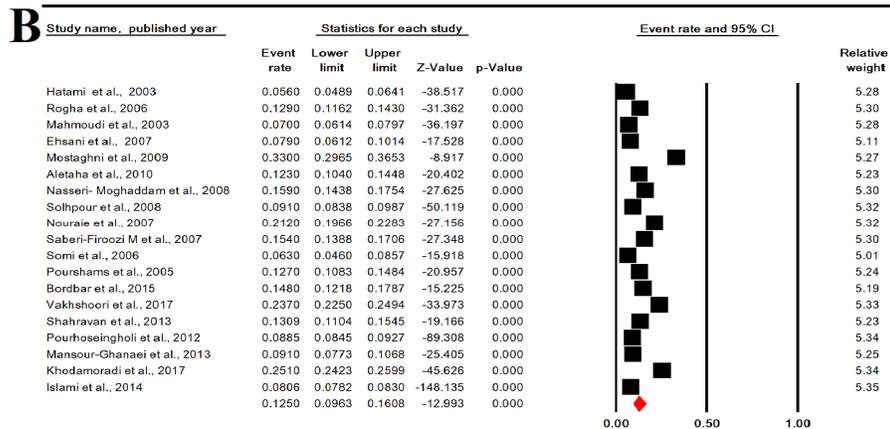
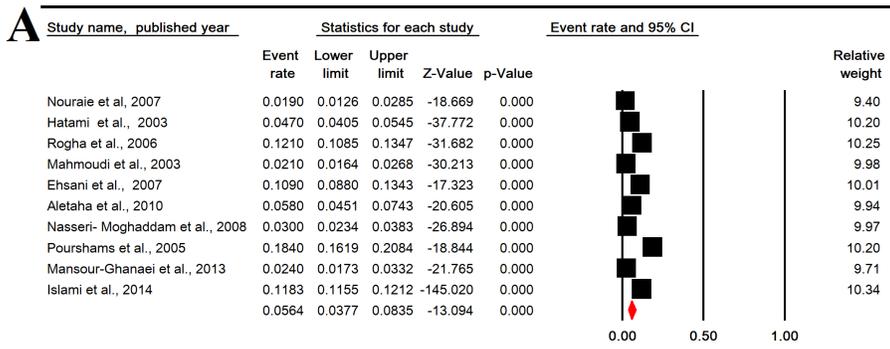
# Figures



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097

Figure 1

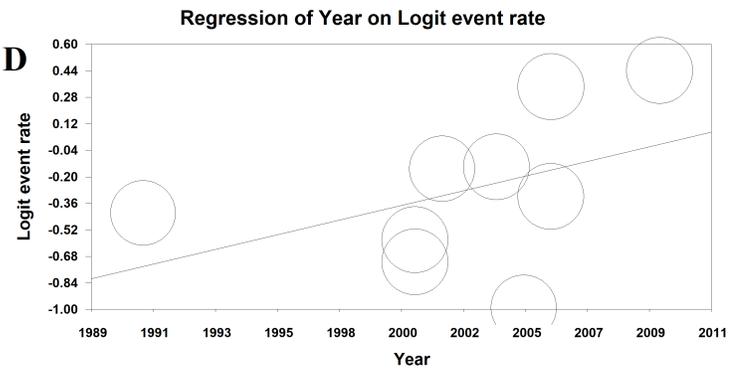
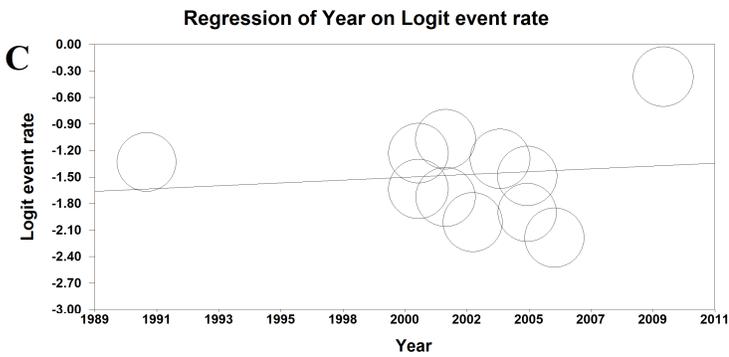
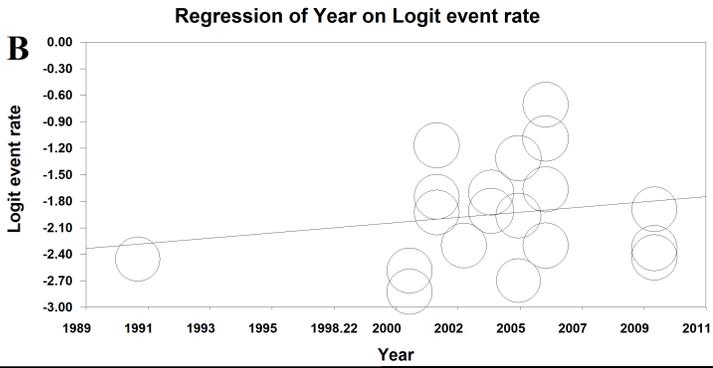
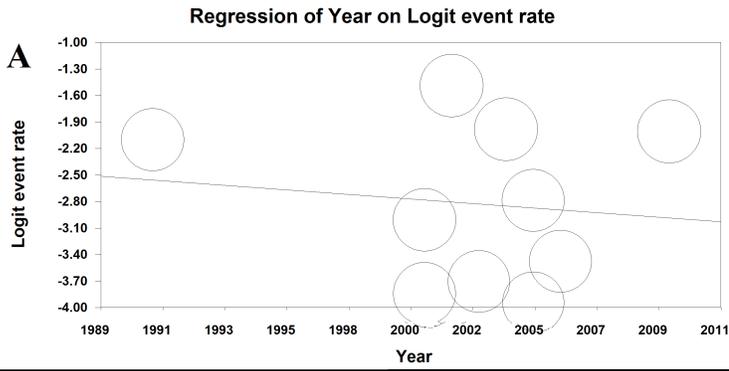
PRISMA process



Meta Analysis

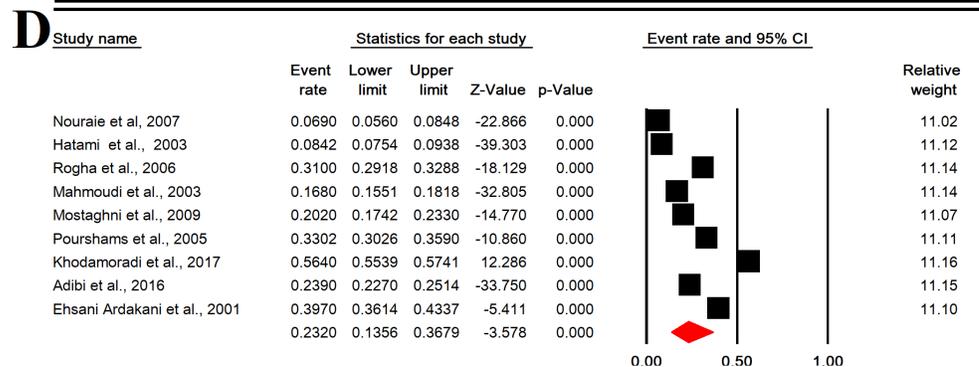
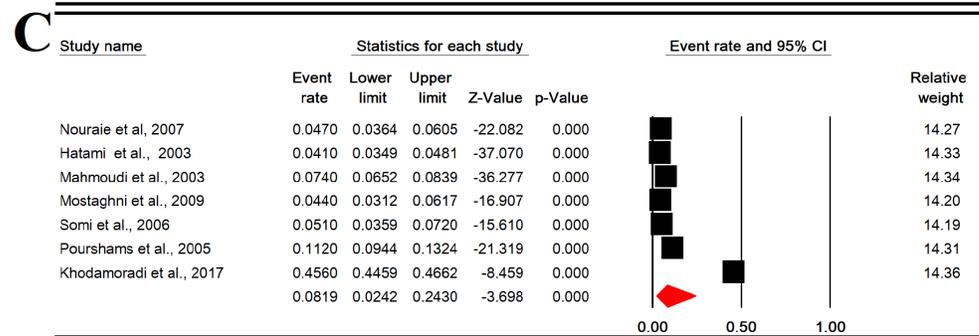
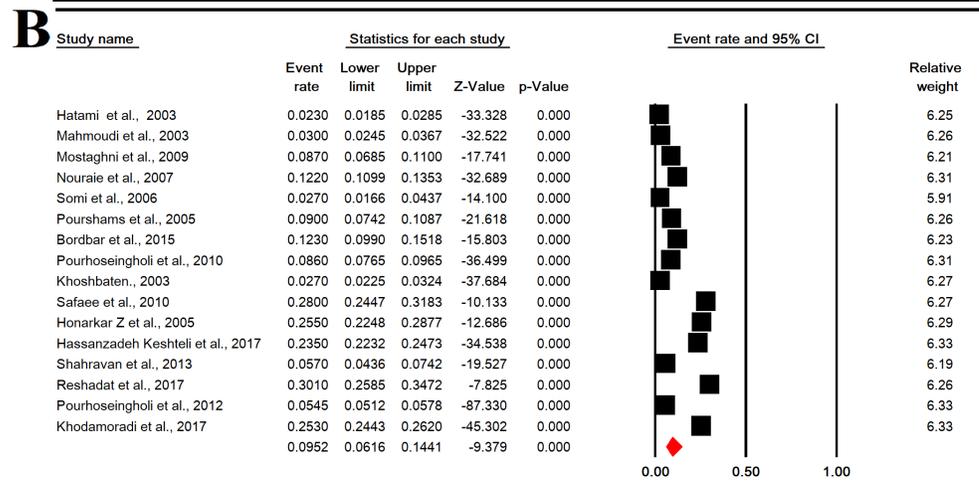
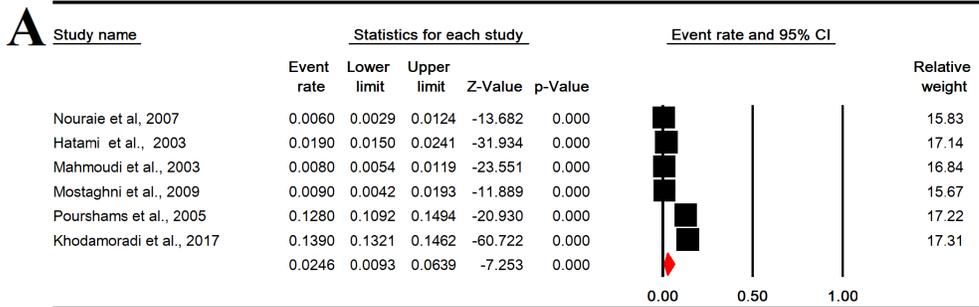
**Figure 2**

The daily (A), weekly (B), monthly (C), and overall (D) prevalence of GERD symptoms in Iranian population



**Figure 3**

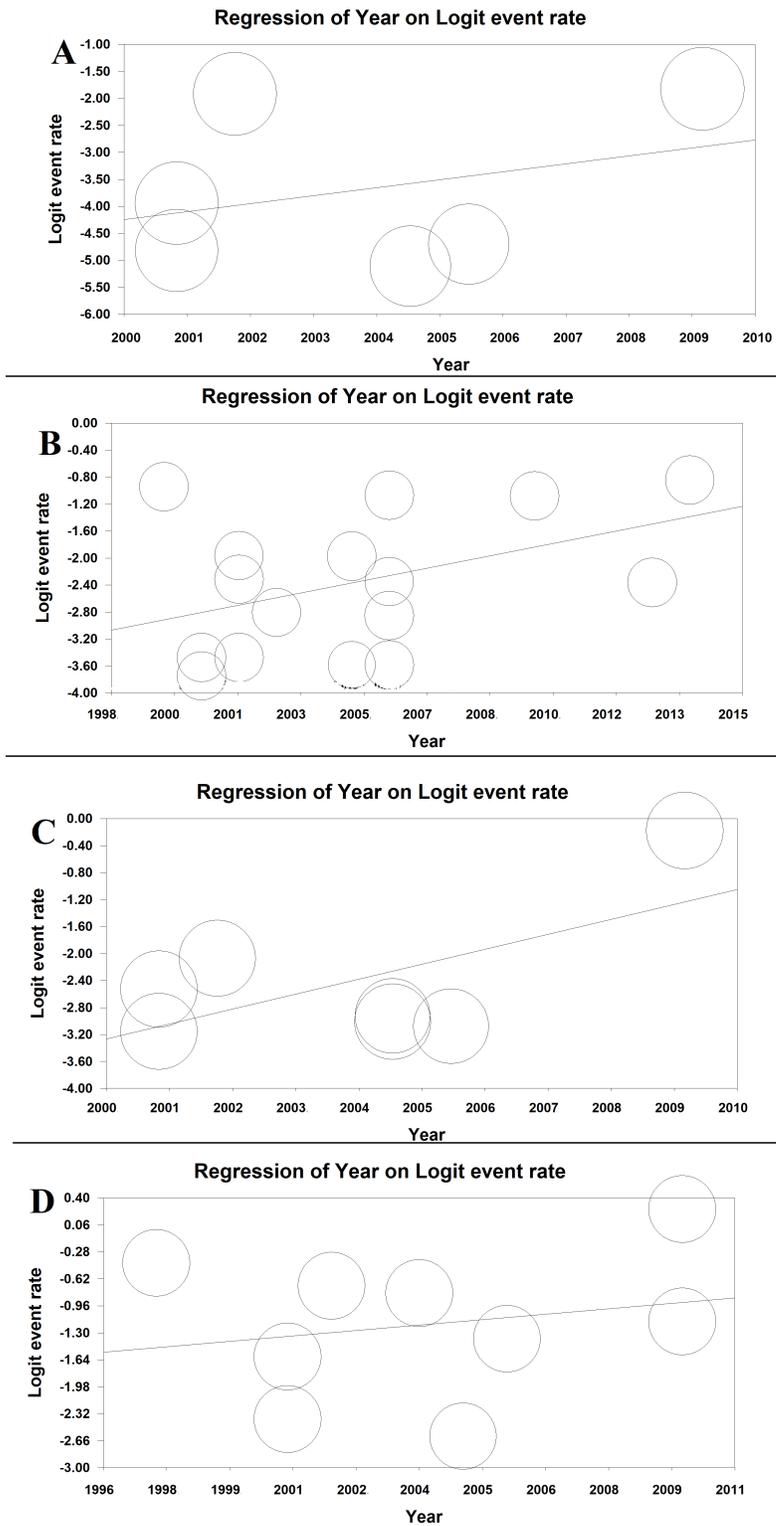
The meta-regression model based on years of study for daily (A), weekly (B), monthly (C), and overall (D) prevalence of GERD



Meta Analysis

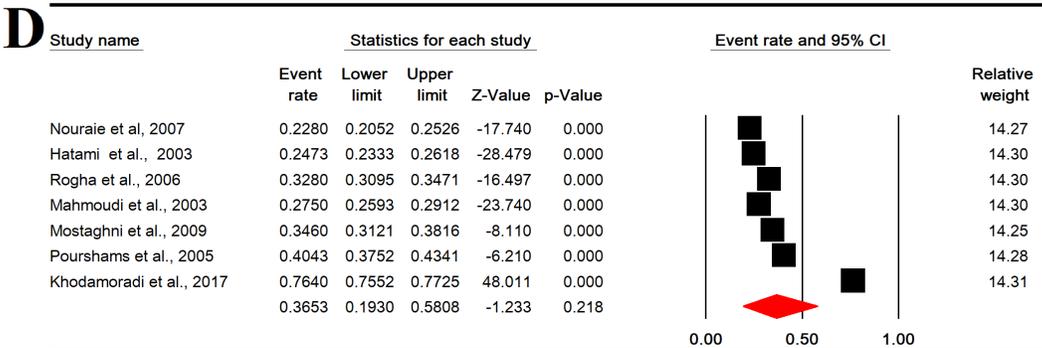
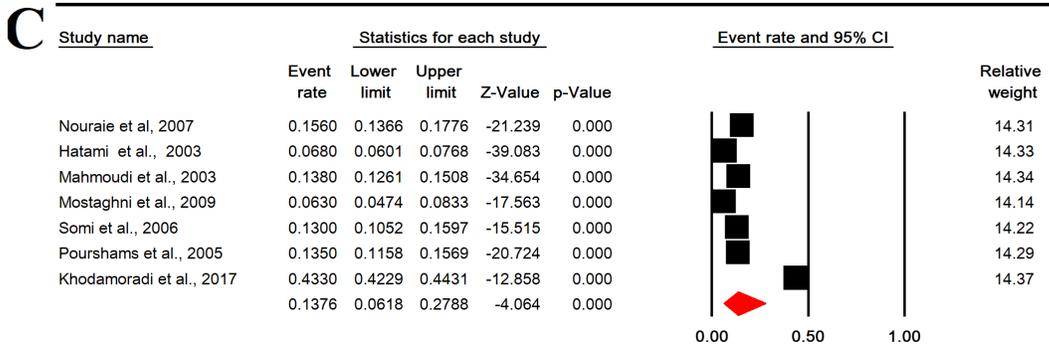
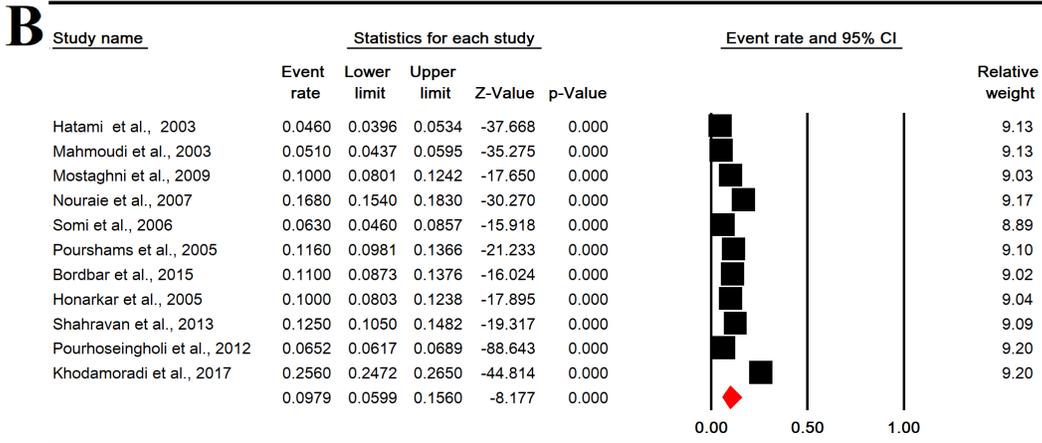
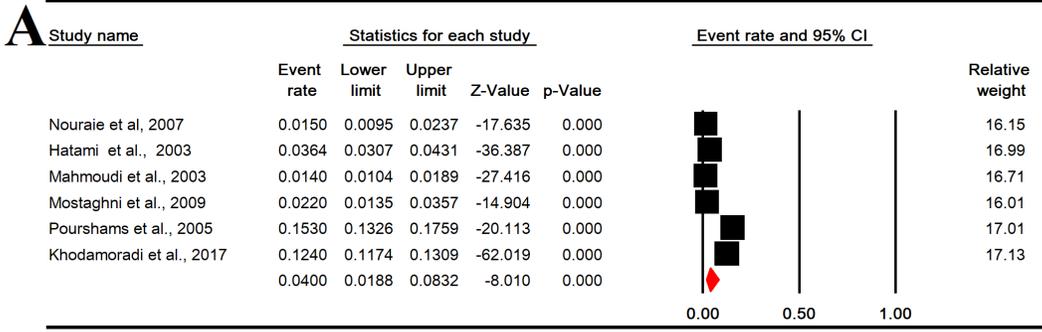
**Figure 4**

The daily (A), weekly (B), monthly (C), and overall (D) prevalence of heartburn in Iranian population



**Figure 5**

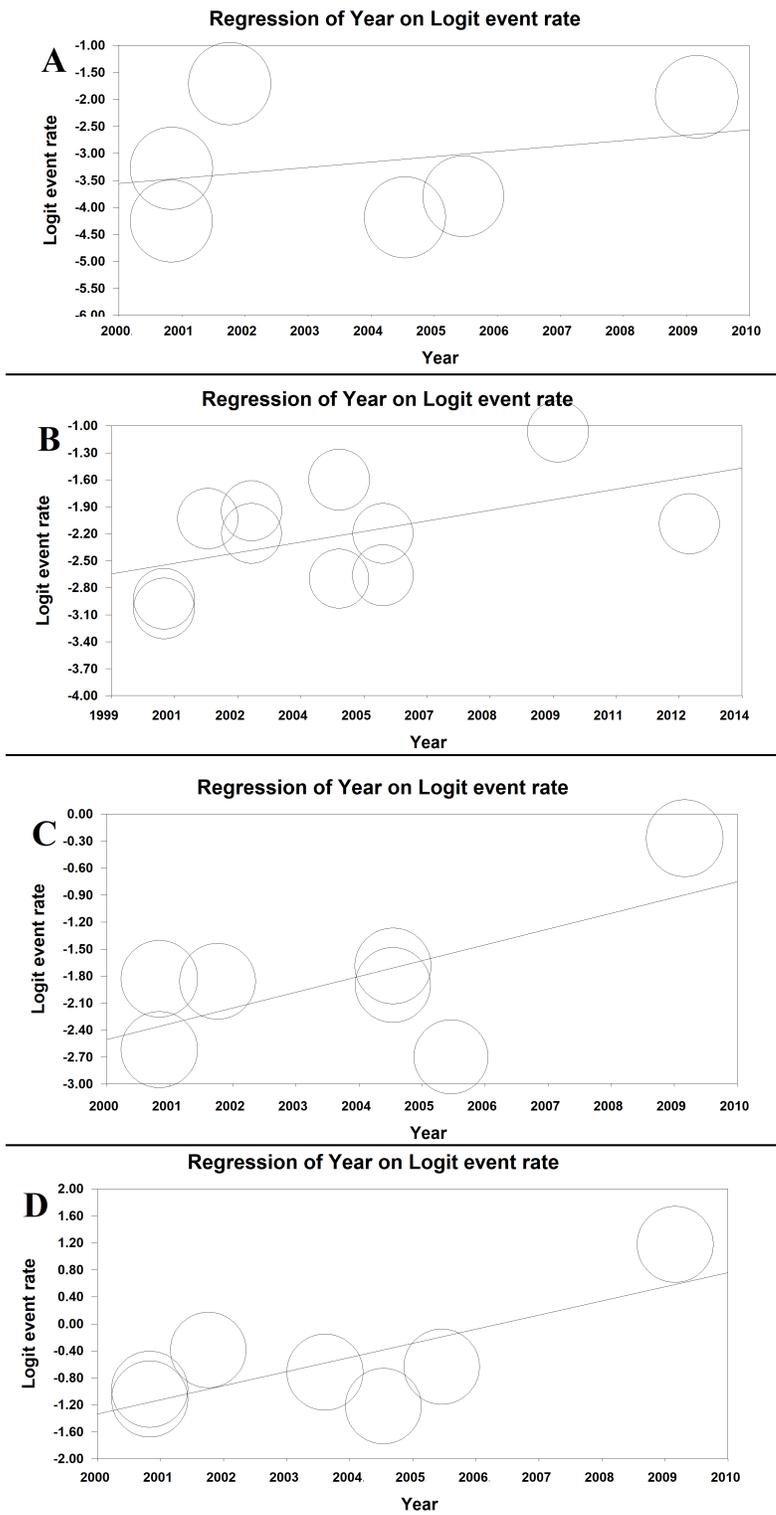
The meta-regression model based on years of study for daily (A), weekly (B), monthly (C), and overall (D) prevalence of heartburn



Meta Analysis

Figure 6

The daily (A), weekly (B), monthly (C), and overall (D) prevalence of regurgitation in Iranian population



**Figure 7**

The meta-regression model based on years of study for daily (A), weekly (B), monthly (C), and overall (D) prevalence of regurgitation

## Supplementary Files

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