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Prevalence of celiac disease among the Iranian population: A systematic review and meta-analysis of observational studies

INTESTINE

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Original Article

ABSTRACT

Background/Aims: The current systematic review and meta-analysis study assessed the prevalence of celiac disease (CD) in Iran.

Materials and Methods: Electronic databases, including MEDLINE, SCOPUS, Web of Science, Cochrane library Collaboration, and Iranian scientific databases, were searched from 1993 to 2013 for English and Persian articles. The following terms were used, alone or combined, "celiac (MeSH)," "ceoliac," "prevalence (MeSH)," and "Iran*." Heterogeneity was assessed using the I^2 statistic with a cut-off value of 50%, and the Chi-square test was used to define a statically significant degree of heterogeneity with a p value of <0.10. The publication bias of literatures was assessed by visual examination of the funnel plot and Begger's funnel plot.

Results: Meta-analysis was conducted on seven publications with 9,720 subjects. Overall, the pooled prevalence of CD among the Iranian population was 0.72% [95% confidence interval (CI): 0.62%–0.98%]. There was no significant heterogeneity among the studies (I2=4%, p=0.396). The pooled prevalence of CD on the basis of IgA-anti tissue transglutaminase (tTGA) and tTGA and duodenal biopsy positivity was 0.83% (95% CI: 0.69%–1.14%) and 0.79% (95% CI: 0.66%–1.09%), respectively. No significant publication bias was observed using the funnel plot and Begger's funnel plot.

Conclusion: CD prevalence among the Iranian population was approximately similar to that of the American and European populations.

Keywords: Celiac, gluten sensitivity disease, prevalence, Iran

INTRODUCTION

Celiac disease (CD) is a life-long immune-mediated disease of the small intestine, resulting from gluten ingestion in genetically predisposed individuals (1). CD symptoms considerably vary from person to person. People with CD may have gastrointestinal symptoms, such as diarrhea, vomiting, weight loss, steatorrhea, extra-intestinal symptoms, fatigue, irritability, depression or anxiety, dermatitis herpetiformis, anemia, neurological problems, osteoporosis, and dental enamel hypoplasia or no symptoms (2-4). CD can occur at any age; however, peak incidence of CD is observed in the fifth decade of adults. CD commonly affects females more than males with a ratio of 3:1 (5).

Gluten is the main protein fraction in wheat, rye, and barley that induces CD. The agriculture spreading pattern can likely describe CD incidence in different countries; for example, CD prevalence is high in some Indian states because wheat is the staple diet in those regions (6). Iran is one of the countries that has the highest rank in per capita wheat consumption in worldwide (7,8). It is expected that the spread of wheat consumption makes a negative pressure on

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Table 1. Quality assessment items

Items	Description
Study scope	Is the study scope (urban and rural) clearly reported?
Sampling method*	Is the sampling method (simple random and multistage random sampling) clearly described?
Included participants characteristics*	Are the characteristics of the participants (sex, age, etc.) clearly described in the study?
Diagnostic testing	Are the diagnostic tests clearly described?
Serology test*	Does the study use serology tests for diagnosing celiac disease?
Duodenal biopsy test*	Does the study use duodenal biopsy for diagnosing celiac disease?
Participants with positive serology test*	Is the number (percent) of participants with positive serology test described?
Participants with positive duodenal biopsy test*	Is the number (percent) of participants with positive duodenal biopsy test described?
Cut-off values of the serology tests	Have the cut-off values of the serology tests been reported?
Marsh classification	Is the Marsh classification described?
Prevalence*	Is the number of participants with celiac disease clearly described?

*If any of these items had not been reported, the study was excluded from the meta-analysis.

CD-predisposing genes, such as HLhuman leukocyte antigen b8 (HLA-B8), that contribute to CD development (7).

The HLA genotype has contributed to the genetic risk factors for CD incidence (9). The results of previous studies revealed that 90% of European patients with CD have human leukocyte antigen DQ2 (LA-DQ2) molecules (9) and the frequency of DQ2 is high in the western European population (8). Afterward, the total frequency of DQ2 decreases from the West to East with low rates among the south-east population, with the virtual absence of CD observed in Japan (4).

With respect to the high wheat consumption in Iran and the decreasing rate of DQ2 frequency from the West to East, it is estimated that CD prevalence is higher in Iran than in European and western countries. Several studies were performed regarding CD prevalence in Iran among various groups; however, the results of these studies are inconsistent (10-14), and thus, true CD prevalence in Iran remains unclear. Therefore, we aimed to conduct a systematic review and meta-analysis of the current epidemiological data regarding CD prevalence in the Iranian population.

MATERIALS AND METHODS

Search strategy

Electronic databases, including MEDLINE (National Library of Medicine), SCOPUS, Web of Science (Thomson Reuters; New York, USA), Cochrane library (Cochrane Collaboration; Oxford, United Kingdom), and Iranian scientific databases [Scientific Information Database (SID), IranMedex, Irandoc, Magiran, and Medlib], were searched from 1993 to 2013 for English and Persian literature. The following terms were used, alone or combined: "celiac (MeSH)," "ceoliac," "prevalence (MeSH)," and "Iran". We applied the Persian equivalents of the English terms for the Iranian database. The list of references of articles was also reviewed for any additional papers. Furthermore, specialized journals and textbooks that were related to the topic were reviewed to gather data on CD prevalence. The data of international organizations (World Health Organization, Centers for Disease Control and Prevention, UNICEF, and Index Medicus for the Eastern Mediterranean Region) about celiac disease were screened. In addition, Gray literatures, such as reports and conference presentations, were considered using the Google search engine.

Study selection

We included a study if it had determined the prevalence or number of people with CD among the normal population. Studies that were not published as full report like conferences abstract and letters to editors, studies of case-report, studies of review or systematic review that not reported any celiac prevalence in Iran.

Research papers were filtered in three steps. In the first and second steps, titles and abstracts of articles were retrieved and reviewed to exclude irrelevant articles. In the third step, full-text articles of the selected abstracts were retrieved to determine relevant articles. Two independent investigators (ZA and GSH) performed the three steps. A third investigator (RH) adjudicated discrepancies between the two reviewers.

Quality assessment

Two independent investigators (ZA and GSH) performed a quality assessment of the eligible articles using the Strengthening the Reporting of Observational Studies in Epidemiology Statement recommendations (15). A third investigator (RH) resolved any discrepancy between investigators. The items of quality assessment were shown in Table 1. If any of the items, i.e., sampling methods, participants' characteristics, type of diagnostic test, number of participants with positive serology or duodenal biopsy, and CD prevalence, were not reported in a study, it was excluded from the meta-analysis.

Data extraction

The following data were extracted from all relevant articles: general information regarding the study (study design, sampling method, number of center, and study scope), data of study participants (age, sex, sample size, and inclusion and exclusion criteria of participants), diagnostic criteria of CD (serology and duodenal biopsy), and number of patients with CD based on diagnostic criteria. We estimated CD prevalence on the basis of IgA-anti tissue transglutaminase (tTGA) and tTGA and duodenal biopsy positivity.

Statistical analysis

Data were presented as numbers and proportions. Heterogeneity was assessed using the I^2 statistic with a cut-off value of 50%, and the heterogeneity of studies was determined using the Chi-square test with a statistical significant level of <0.10. Statistical analyses were performed using STATA version 11.0 (STATA Corp; College Station, Texas, USA). Pooled prevalence and 95% confidence interval (CI) were calculated using a fixed-effect model. Sensitivity analysis was conducted on the basis of the participants' age and diagnostic tests. The publication bias of literatures was assessed by visual examination of the funnel plot and Begger's funnel plot.

RESULTS

The electronic databases search identified 1,602 citations (including 753 duplicates). In the title and abstract evaluation step, 828 articles were excluded. The reason for excluding a large number of articles was that in the Iranian scientific database (SID, IranMedex, Irandoc, Magiran, and Medlib), we could just search with single terms; thus, many irrelevant articles found in this manner were excluded from the systematic review during this step. Twenty-one full-text articles were assessed; of these, 10 articles were eligible for the systematic review (four Persian and six English articles) (10-14,16-20). Detailed characteristics of each study are shown in Table 2. Three articles were excluded during quality assessment (10,16,18) because the sampling method was not described. Finally, seven articles were included in the meta-analysis, of which two research studies were conducted among children (11,12) and five among adults (13,14,17,19,20). Figure 1 shows detailed information regarding the study selection process.

Thirty dissertations were found via the Google search engine and Iranian database (Irandoc); all of them were irrelevant, and thus, were excluded from the systematic review. Thirty research projects that were related to CD were also identified, of which 21 were published and we had captured them during the electronic search. We contacted the authors of unpublished research projects via e-mail to obtain relevant data, but none of them replied.

The mean age at which the disease was diagnosed was 32.04±1.69 years, and 3,891 (50.9%) and 3,755 (49.1%) were female and male, respectively. Overall, pooled CD prevalence among the general population was 0.72% (95% CI: 0.62%–0.98%). There was no significant heterogeneity among the studies (I^2=4%, p=0.396) (Figure 2).

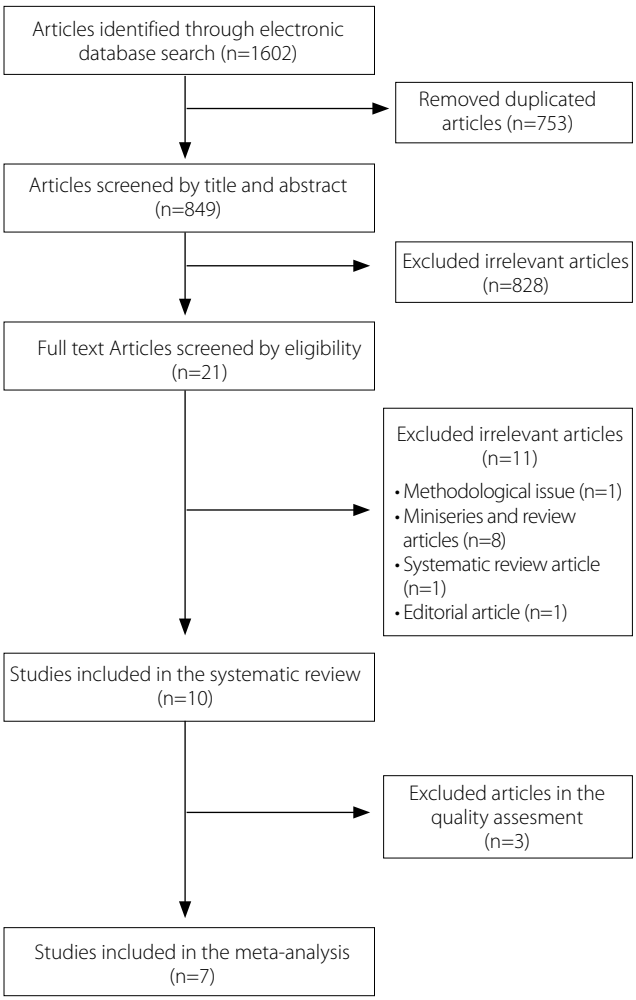

Figure 1. Flow diagram of the systematic review.

We also considered sensitivity analysis on the basis of the diagnostic test and age of participants. Two studies reported that CD prevalence ranged from 0.5% (12) to 0.6% (11) among children, and five studies were conducted among adults. We conducted another analysis on the basis of the diagnostic test. With respect to tTGA, pooled CD prevalence was 0.83% (95% CI: 0.69%–1.14%) among the Iranian adult population. Heterogeneity was not statistically significant among the studies (I^2=29.8%, p=0.2). With respect to tTGA and duodenal biopsy positivity, pooled CD prevalence was 0.79% (95% CI: 0.66%–1.09%).

The funnel plot revealed a symmetric pattern (Figure 3) that suggested no publication bias in our meta-analysis. Furthermore, no publication bias was found using the Begger's funnel plot (Figure 4).

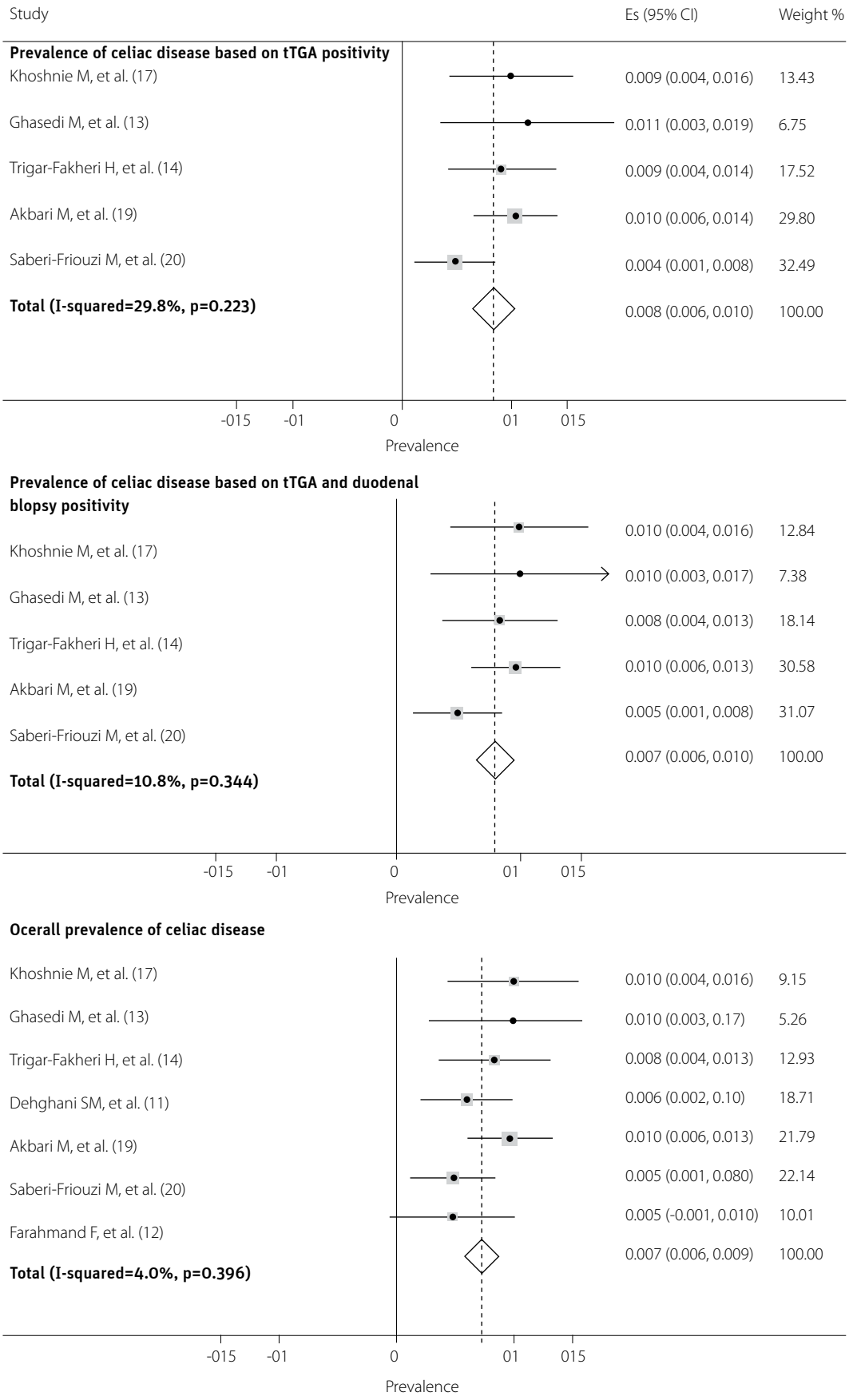

Figure 2. Prevalence of celiac disease.

DISCUSSION

We conducted a systematic review and meta-analysis of studies addressing CD prevalence among the general Iranian population. We found 1,602 literatures through an electronic database search (including 753 duplicates). During title/abstract and full-text evaluations, 838 articles were excluded because in a large number of articles that was found in the Iranian scientific database, we could just search with single terms. Ten articles were eligible for the systematic review. Of those, seven articles were included in the meta-analysis. Moreover, theses and research projects were found and assessed, but no extra data were obtained.

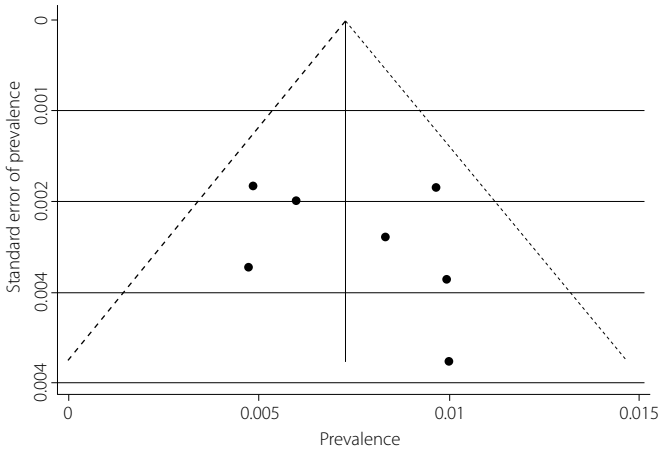

Figure 3. Funnel plot of celiac disease prevalence for a meta-analysis of seven studies.

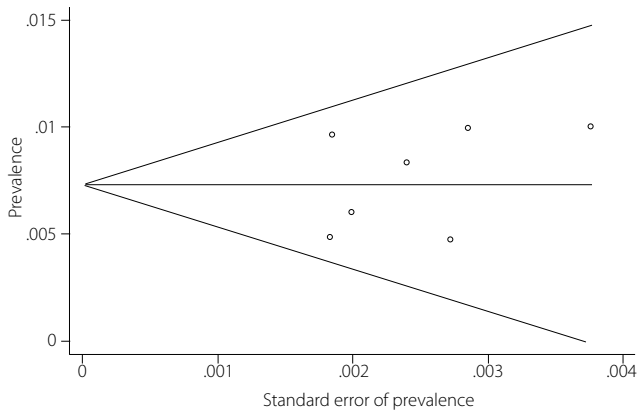

Figure 4. Begger's funnel plot of celiac disease prevalence for a meta-analysis of seven studies.

CD prevalence among the general Iranian population ranged from 0.5% (12,20) to 1.0% (13,17,19). Our results revealed that the overall pooled CD prevalence among the Iranian population was 0.72%. Studies were segregated according to the age of participants and the type of diagnostic test. CD prevalence among Iranian children was between 0.5% (12) and 0.6% (11). In Europe and United States, CD prevalence is 0.3%–1.25% among children (21), and in Turkey, Saudi Arabia, and Tunisia, CD prevalence is 0.6%, 2.2%, and 0.6%, respectively, among children (22-24). CD-associated diseases, such as type I diabetes, thyroiditis, ataxia, osteopenia, and depression, which were mostly described in adults, can certainly be observed in children (25). Because of the high level of importance of CD in children and a small number of studies related to CD prevalence among Iranian children, it is necessary to conduct more studies to assess CD prevalence among Iranian children.

In our meta-analysis, we categorized studies among Iranian adults with respect to the diagnostic test. Pooled CD prevalence based on tTGA and tTGA and duodenal biopsy positivity was 0.83% and 0.79%, respectively. CD affects approximately 0.5%-1% of the world population (4). CD prevalence in the general population of the United States, Europe, and Africa is 0.5%–1.0% (26), 1%, and 0.28%–5.6%, respectively (4). In Iran, planet foods are the main component of diet, and Iran ranks as one of the top wheat-consuming population worldwide, with per capita consumption of up to 160 kg/year (7,8). As a result, the continuous

Table 2. Summary of characteristics of studies included in the systematic review

Author, publication year	Number of participants	Mean age of participants (years)	Number of patients with CD	CD prevalence	AGA-IgA+	EMA+	tTG+	Duodenal biopsy+
Shahbazkhani et al. (16)	2000	35.5	12	0.6	49	12	-	12
Tirgar-Fakheri et al. (14)	1438	35.5	12	0.8	-	-	13	12
Khoshnia et al. (17)	1209	50	12	1.0	-	-	12	8
Joshaghani et al. (18)	2547	30.1	28	1.1	-	-	28	-
Akbari et al. (19)	2799	33.7	27	0.9	-	5	29	27
Ghasedi et al. (13)	700	42.5	7	1.0	-	-	8	7
Saberi-Firouzi et al. (20)	1440	45.3	7	0.4	-	2	7	5
Bahari et al. (10)	1600	33.2	14	0.8	-	-	14	10
Farahmand et al. (12)	634	12.8	3	0.5	-	-	3	3
Dehghani et al. (11)	1500	9.5	9	0.6	-	-	30	9

Studies were ordered with respect to the publication year.
CD: celiac disease; AGA: anti-gliadin antibodies; IgA: immunoglobulin A; IgG: immunoglobulin G; EMA: anti-endomysial antibodies; tTG: anti-transglutaminase antibodies; +: positive; -: data not available

and high level of exposure to wheat protein has likely increased the risk of CD incidence. In our study, CD prevalence among the Iranian population was similar to that among the European and western country populations; this can be because of the lack of knowledge and awareness of CD, attribution of CD symptoms to other similar disease, and low suspicion of CD among physicians in Iran (16,27). For example, results revealed that 12% of patients with irritable bowel syndrome have CD for many years (28). Because some patients with CD remain undiagnosed for years due to a wide range of clinical symptoms and lack of a standard clinical profile for CD, which imposes a high burden on medical care system, cost-effective policies of diagnosing and screening patients could reduce the morbidity and mortality associated with untreated CD.

Our results revealed no significant publication bias. Publication bias was minimized by conducting wide searches through multiple databases in our meta-analysis.

One of the limitations of our study was the small number of research studies conducted among adults and children. Moreover, there was a discrepancy among studies in terms of the cut-off values of celiac serological tests. However, to the best of our knowledge, the present systematic review and meta-analysis was the first study to assess CD prevalence among the general Iranian population. Although investigators were not blind to the authors, institutions, journals, and other relevant information, two independent reviewers completed the process of study selection, and the third reviewer resolved all discrepancies, which minimized the likelihood of a bias.

In conclusion, the myth that CD is a common disease only in European and other western countries is currently not true. There is a requirement for increasing the awareness and identifying all CD subtypes among all age group in the Middle East countries, particularly Iran. Further population surveys addressing both symptomatic and asymptomatic groups in different age groups would help in discovering other proportions of the disease in Iran.

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Informed Consent: N/A.

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