Celiac disease in Iran: a systematic review and meta-analysis

Roghayeh Mohammadibakhsh¹, Rahim Sohrabi², Morteza Salemi³, Masood Taheri Mirghaed⁴, Masoud Behzadifar⁵

¹Ph.D. Student of Health Policy, Hamadan University of Medical Sciences, Hamadan, Iran
²Ph.D. Student of Health Policy, Iranian Social Security Organization, Zanjan Province Health Administration, Zanjan, Iran
³Ph.D. Student of Health Policy, Social Determinants in Health Promotion Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
⁴Ph.D. Student of Health Policy, Department of Health Services Management, School of Health Management and Information Sciences, Iran University of Medical Sciences, Tehran, Iran
⁵Ph.D. Student of Health Policy, Health Management and Economics Research Center, Iran University of Medical Sciences, Tehran, Iran

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Abstract

Introduction: Celiac disease (CD) is a chronic autoimmune-mediated disorder with both intestinal and systemic manifestations. The aim of this study was to determine the prevalence of celiac disease in Iran.

Methods: We conducted a systematic search on Embase, Pub Med, Web of Science, Google Scholar, MagIran, Scientific Information database (SID) and Iranmedex from 2003 through to November 2015. The Der-Simonian/Laird’s (DL), with a 95% confidence interval employed to estimate the overall pooled prevalence. Heterogeneity was investigated by using subgroup analysis based on sample size and time of study.

Results: Sixty-three studies with 36,833 participants met inclusion criteria for analysis. The overall prevalence of celiac disease in 63 studies that had used serological tests for the diagnosis was observed as 3% (95% CI: 0.03-0.03) and the overall prevalence of celiac disease in studies that had used biopsy method for diagnosis was observed as 2% (95% CI: 0.01-0.02).

Conclusion: The prevalence of celiac disease in Iran was similar or even higher than world-wide reported.

Keywords: Prevalence, Meta-analysis, Celiac disease, Iran, Systematic review

1. Introduction

Celiac disease (CD) is one of the most important malabsorption diseases caused by sensitivity to gluten grains in the small intestine. This disease causes inflammation in the small intestine and it can impede the absorption of nutrients (1). Gluten can be found in cereals such as wheat and barley (2). This disease can occur at any age (1). Celiac disease can cause symptoms such as weight loss, growth retardation, osteoporosis, anemia, classic symptoms of malabsorption, chronic constipation, abdominal pain and metabolic bone diseases in patients (3). Signs of mental illness such as depression and cognitive impairment are variable in this disease (4). There are several ways to diagnose celiac disease and using Anti-Tissue Transglutaminase and duodenal biopsy (1). Various studies around the world have investigated the prevalence of celiac disease. IgA-class tissue transglutaminase antibody test has been used in most of these studies. Prevalence of celiac disease in populations of America and Europe has been reported nearly 1% (5-9). In studies carried out in Finland, Sweden and Mexico based on serology and duodenal biopsy in the general population, the prevalence of celiac disease has been reported about 1% (10-12). Also in studies conducted on different individuals based on serology, prevalence rate has been reported as 0.7% in Italy, and 0.3% in Germany (13). Celiac disease in countries of Eastern Mediterranean Region Organization (EMRO)
including North Africa and the Middle East are increasingly on the rise (6, 14-17). Accordingly, it has imposed a lot of economic costs on the respective countries (18). In some studies, this disease has been diagnosed two to three times more in women than in men (19). However, in studies carried out in the general population, a significant difference was not observed between the prevalence of the disease in both sexes (7, 9). Increased prevalence of celiac can be due to the high sensitivity of serological tests and more attention to this disease. If just a clinical method is used to diagnose this disease, a large proportion of people may not be diagnosed with the disease (20). Thus, this systematic review and meta-analysis study was conducted to assess the prevalence of celiac disease in Iran. The results may also be helpful in enlightening researchers and policy makers for adopting effective policies and programs to reduce the prevention and prevalence of celiac disease.

2. Material and Methods
2.1. Search methods
To perform this study and find the related studies, Embase, Pub Med, Web of Science, Google Scholar, MagIran, Scientific Information Database (SID) and Iranmedex databases were searched to December 2015. Searching for studies was carried out in two languages of English and Persian. Moreover, conferences related to celiac disease, and the reference lists of studies were also assessed. For finding the related studies, the keywords based on Medical Subject Headings (MeSH) were used and the search strategy in databases was applied according to title and abstract as “Prevalence” OR “Frequency” AND “Celiac Disease” OR “coeliac disease” AND “Iran”.

2.2. Study selection
All Iranian population-based studies in which the prevalence of celiac disease has been reported, the studies in which the diagnostic methods including serological tests and a biopsy of the duodenum have been used according to the Marsh classification (21) and those that their results clearly suggest the prevalence of celiac, were selected as inclusion criteria. Moreover, some researches with the following characteristics were excluded from the study:
1) Case Report, Case Series and Quasi-Experimental studies.
2) Those which lacked appropriate data for estimating prevalence.
3) The studies not conducted based on population.
4) Case Report, Case-Series, Quasi-Experimental and Letter of Editor studies.
5) The studies not applied standard diagnostic method and those with unclear results.
6) Those conducted on non-Iranian population.

2.3. Data collection
Two authors independently evaluated title and abstract of studies based on inclusion and exclusion criteria. To increase the quality of the studies, blinding method was used and the authors’ names and the journal characteristics were hidden. If there is disagreement between the authors about studies, a third person was asked to act as a judge and resolve disagreements with discussion. The agreement between the two authors to extract information was 95.2% and the agreement was 81.5% based on Kappa reliability statistics. After reviewing the studies and finding original studies to analyze, the information contained the name of the first author, year of publication, place of study, the average age in years, the number of positive people by serological test, the number of positive people were extracted by serological test and the number of positive people by duodenal biopsy according to Mesh classification and the type of studies were extracted. All reviews and analyses on literature were conducted based on the PRISMA guidelines.

2.4. Quality assessment of studies
After finding studies, the STROBE check list (22) was used to assess their quality. According to items of this checklist, the studies that had all the desired items were classified with high quality, those which lacked two of the items with medium quality and those which lacked more than two items were classified as low quality studies. No study with low quality was excluded. The mean score of all studies was 15.75.

2.5. Statistical analysis
In this meta-analysis, the prevalence was calculated based on Der-Simonian / Laird’s (DL) test, using random effects model (23). The findings were presented in Forest Plot graph. All data were reported with 95% confidence intervals based on random model. To assess heterogeneity between studies, statistical tests I2 and Q-test (24) were used. P-value of less than 0.05 was considered as statistically significant amount. To explore sources of heterogeneities, variables such as publishing year of studies, geographic area of study, sample size, quality of studies and individuals’ age were subject to sub-group analysis. Also, to explore more sources of heterogeneity, some
effective factors such as publishing year and participants’ age were meta-regressed according to prior defined variables. To assess publication bias, Egger and Begg tests (25, 26) were used. Studies data were given to the Stata 12.0 software (StataCorp LP, College Station, TX) and analyzed.

3. Results
In the initial search on databases and reference lists search, 520 studies were eligible, of which, 269 studies were duplicate items. According to the survey conducted on the remaining studies, 93 studies were excluded because of lack of relevance on the subject. The full texts of the 158 studies were investigated. Finally, 63 studies were entered to meta-analysis phase (27-89). Figure (1) shows PRISMA flowchart of selecting the studies.

3.1. Characteristics of the included studies
The number of participants in these studies was 36,833. Mirzaagha’s study of 2,999 participants in Golestan province was the largest, and Najafi’s study with 64 participants in Tehran province, was the smallest study. Studies were conducted between years 2003 and 2015. The participants’ age in these studies varied between 5-57 years. Table (1) shows the characteristics of the included studies.

3.2. Quality of studies
After checking quality of included studies based on the STROBE checklist, 25 of them (39.6%) were of high-quality, 22 papers (34.9%) were of average quality and 16 papers (25.5%) were of low quality.

3.3. Prevalence of celiac disease
The overall prevalence of celiac disease in 63 studies that had used serological tests for the diagnosis, was observed as 3% (95% CI: 0.03-0.03, I2: 90.9%) (Figure 2). The number of participants in this study was 36,833. Besides, the overall prevalence of celiac disease in 41 studies that had used biopsy method for diagnosis, was observed as 2% (95% CI: 0.01-0.02, I2: 87.7%) (Figure 3). The number of participants in this study was 24,538.
Table 1. Characteristics of studies included

| Author               | Year | City         | Age | Sample size | Type of study   | Quality of study |
|----------------------|------|--------------|-----|-------------|-----------------|-----------------|
| Shahbazi Khania      | 2003 | Tehran       | 35.5| 2000        | Cross-sectional | Intermediate    |
| Shahbuzkhani        | 2004 | Tehran       | 18.7| 250         | Cross-sectional | Low             |
| Shahbuzkhania       | 2004 | Tehran       | 31  | 100         | Cross-sectional | High            |
| Ate Yasin           | 2004 | Tehran       | 29.55| 250        | Case-control    | Intermediate    |
| Tirgar-Fakheri      | 2004 | Sari         | 35.5| 1438        | Cross-sectional | Intermediate    |
| Farahmand           | 2004 | Tehran       | 13.9| 35          | Cross-sectional | Intermediate    |
| Nikpour             | 2005 | Tehran       | 39  | 400         | Cross-sectional | Intermediate    |
| Khoshnia            | 2005 | Gonbad-Kavoos| 50  | 1209        | Cross-sectional | Intermediate    |
| Sheikhholeslami     | 2005 | Ghazvin      | 31.87| 120        | Case-control    | Intermediate    |
| Akbari              | 2006 | Kerman-Sari  | 33.7| 2799        | Cross-sectional | Intermediate    |
| Joshaghani          | 2006 | Golestan     | 30  | 2547        | Cross-sectional | Intermediate    |
| Masoodi             | 2007 | Bandar Abbas | 36.7| 150        | Cross-sectional | High            |
| Nikpour             | 2007 | Tehran       | 40.3| 126         | Prospective     | Low             |
| Inati               | 2008 | Tehran       | 25.55| 250        | Case-control    | Intermediate    |
| Saberi-Firouzi      | 2008 | Shiraz       | 45.3| 1440        | Cross-sectional | Intermediate    |
| Hashemi             | 2008 | Ahvaz        | 16.8| 104         | Cross-sectional | High            |
| Dehghani            | 2008 | Shiraz       | 9.8 | 72          | Cross-sectional | High            |
| Emami               | 2008 | Tehran       | 35.3| 270         | Cross-sectional | Low             |
| khoshbaten          | 2008 | Tabriz       | 25.35| 250        | Case-control    | Intermediate    |
| Zamani              | 2009 | Tehran       | 36.7| 288         | Cross-sectional | High            |
| Rostami-Nejad       | 2009 | Tehran       | 36  | 411         | Cross-sectional | High            |
| Ghahramani          | 2009 | Arak         | 40  | 810         | Case-control    | Low             |
| Kashkabaten         | 2009 | Tabriz       | 37  | 300         | Cross-sectional | Low             |
| Bahariz             | 2010 | Zahedan      | 33.2| 1600        | Cross-sectional | High            |
| Keshavarz           | 2010 | Kermanshah   | 31  | 170         | Cross-sectional | Intermediate    |
| Ghergherehchi       | 2010 | Tabriz       | 9.05| 135         | Cross-sectional | Low             |
| Mirzaagha           | 2010 | Tehran       | 36.5| 2999        | Cross-sectional | High            |
| Sima                | 2010 | Tehran       | 33.7| 112         | Cross-sectional | Low             |
| Shahbuzkhani        | 2010 | Tehran       | 39.7| 100         | Cross-sectional | Low             |
| Farahmand           | 2011 | Tehran       | 7.18| 301         | Cross-sectional | High            |
| Rahimi              | 2011 | Tehran       | 40.56| 316        | Cross-sectional | High            |
| Norouzinia          | 2011 | Tehran       | 26  | 796         | Cross-sectional | Intermediate    |
| Rostami-Nejad       | 2011 | Tehran       | 36.1| 407         | Cross-sectional | Low             |
| Bashiri             | 2011 | Kermanshah   | 18  | 241         | Cross-sectional | High            |
| Inaloo              | 2011 | Shiraz       | 10.6| 1600        | Case-control    | Intermediate    |
| Akhondi-Meybodi     | 2011 | Yazd         | 29.85| 125       | Cross-sectional | Low             |
| Farahmand           | 2012 | Tehran       | 12.8| 634         | Cross-sectional | High            |
| Bakshhpour          | 2012 | Zahedan      | 37.4| 364         | Cross-sectional | High            |
| Emami               | 2012 | Isfahan      | 34.3| 324         | Case-control    | Intermediate    |
| Mehrdad             | 2012 | Rasht        | 39.46| 454        | Cross-sectional | Low             |
| Khoshbaten          | 2012 | Tabriz       | 37  | 200         | Cross-sectional | High            |
| VosoghiniaI         | 2012 | Mashhad      | 19.78| 87        | Cross-sectional | Intermediate    |
| Bakshhpour          | 2013 | Zahedan      | 37.4| 403         | Cross-sectional | High            |
| Amini-Ranjbar       | 2013 | Kerman       | 6   | 144         | Cross-sectional | High            |
| Dehghani            | 2013 | Shiraz       | 9.5 | 1500        | Cross-sectional | High            |
| Houshiyar           | 2013 | Ardabil      | 31.4| 105         | Cross-sectional | Low             |
| Jafarabadyarlo      | 2013 | Ilam         | 29.02| 1000      | Cross-sectional | Low             |
| Hayatbakhsh         | 2013 | kerman       | 43  | 2259        | Cross-sectional | Intermediate    |
| Shaykhesmali        | 2013 | Sanandaj     | 35.45| 180       | Case-control    | Low             |
| Ghergherehchi       | 2013 | Tabriz       | 12  | 200         | Cross-sectional | Intermediate    |
| Mahmoodi            | 2014 | Ilam         | 29.02| 1000      | Cross-sectional | High            |
| Shayesteh           | 2014 | Ahvaz        | 31.8| 465         | Cross-sectional | High            |
| Najafi              | 2014 | Tehran       | 8.39| 64          | Cross-sectional | High            |
| Zahmatkeshan        | 2014 | Shiraz       | 5.73| 82          | Case-control    | Intermediate    |
| Honar               | 2014 | Shiraz       | 12.7| 215         | Case-control    | Low             |
| Yazdanbod           | 2014 | Ardabil      | 28.45| 181       | Cross-sectional | Intermediate    |
| Honar               | 2015 | Shiraz       | 10.38| 83        | Prospective     | High            |
| Fallahi             | 2015 | Tehran       | 12  | 96          | Cross-sectional | Low             |
| Ahmadi              | 2015 | kerman       | 34.57| 143        | Cross-sectional | High            |
| Dehghani            | 2015 | Shiraz       | 57.68| 101       | Cross-sectional | Intermediate    |
| Shahramian          | 2015 | Zahedan      | 43.09| 1002      | Case-control    | High            |
| Jandaghi            | 2015 | Tehran       | 35.03| 406       | Case-control    | High            |
| Shahramian          | 2015 | Zahol-Zahedan| 28.81| 620        | Case-control    | High            |
3.4. Results of subgroup analysis

The pooled prevalence was stratified according to age, sample size, the quality of studies, year of publication, and geographic area of studies in Table (2).

3.5. Ages categories and prevalence of celiac disease

The prevalence of celiac disease in studies that had used serological tests for the diagnosis was observed as 3% (95% CI: 0.03 - 0.06) for the age group of less than ten years, 5% (95% CI: 0.03-0.06) for the age group 10 to 20 years, 3% (95% CI: 0.02-0.04) for the age group of 20-30 years, 3% (95% CI: 0.02-0.04) for the age group 30-40 years.
years, 2% (95% CI: 0.03-0.04) for the age group 40-50 years and 4% (95% CI: 0.00-0.04) for the age group 50 to 60 years. The prevalence of celiac disease in studies that had used duodenal biopsy for diagnosis was 2% (95% CI: 0.00-0.04) for the age group less than 10 years, 3% (95% CI: 0.01-0.04) for the age group 10-20 years, 1% (95% CI: 0.01-0.02) for the age group 20-30 years, 2% (95% CI: 0.02-0.03) for the age group 30-40 years, 0% (95% CI: -0.01-0.03) for the age group 40-50 years, and 1% (95% CI: -0.01-0.03) for the age group 50-60 years.

3.6. Sample size and prevalence of celiac disease

The prevalence of celiac disease in studies that had used serological tests for the diagnosis was 4% (95% CI: 0.03-0.05) for studies with the sample size less than 800 participants, 3% (95% CI: 0.02-0.04) for studies with 800 to 1,600 participants, 2% (95% CI: -0.01-0.06) for studies with 1,600 and 2,400 participants, and 1% (95% CI: 0.00-0.02) for studies with more than 2,400 participants. Prevalence of celiac disease in studies that had used the duodenal biopsy for diagnosis was 3% (95% CI: 0.03-0.04) in sample sizes less than 800 participants, 0% (95% CI: 0.00-0.01) for studies with 800-1,600 participants, 1% (95% CI: -0.00-0.01) for studies with 1,600-2,400 participants and 1% (95% CI: 0.01-0.02) for studies with more than 2,400 participants.

3.7. Quality of the studies included and prevalence of celiac disease

The prevalence of celiac disease was observed for high-quality studies that had used serological tests for diagnosis as 3% (95% CI: 0.02-0.04), for studies of medium quality, 5% (95% CI: 0.04-0.07) and for low quality studies, 2% (95% CI: 0.01-0.02). Prevalence of celiac disease in high-quality studies that had used the duodenal biopsy for diagnosis was 3% (95% CI: 0.02-0.03), for studies of medium quality, 1% (95% CI: 0.01-0.01) and for poor quality studies, 4% (95% CI: 0.02-0.06).

| Author          | Year      | City          | Prevalence |
|-----------------|-----------|---------------|------------|
| Shahbazkhania   | 2003      | Tehran        | 0.01       |
| Shahbazkhani    | 2004      | Tehran        | 0.02       |
| Ale Yasin       | 2004      | Tehran        | 0.01       |
| Torgha-Fakhari  | 2004      | Sari          | 0.01       |
| Farahmand       | 2004      | Tehran        | 0.06       |
| Khoshsia        | 2005      | Gonbad-Kavoos | 0.00       |
| Sheikholeslami  | 2005      | Ghazvin       | 0.01       |
| Akiari          | 2006      | Kerman-Sari   | 0.01       |
| Masoodi         | 2007      | Bandar Abbas  | 0.10       |
| Nikpour         | 2007      | Tehran        | 0.06       |
| Saberi-Firoodi  | 2008      | Shiraz        | 0.03       |
| Dehghani        | 2008      | Shiraz        | 0.03       |
| Emami           | 2008      | Tehran        | 0.03       |
| Zamani          | 2009      | Tehran        | 0.01       |
| Rostami-Nejad   | 2009      | Tehran        | 0.07       |
| Bahari          | 2010      | Zahedan       | 0.00       |
| Keshavarz       | 2010      | Kermanah      | 0.07       |
| Mirzaaghah      | 2010      | Tehran        | 0.02       |
| Farahmand       | 2011      | Tehran        | 0.01       |
| Norouzinha      | 2011      | Tehran        | 0.01       |
| Rostami-Nejad   | 2011      | Tehran        | 0.08       |
| Bashiri         | 2011      | Kermanah      | 0.08       |
| Inaloo          | 2011      | Shiraz        | 0.00       |
| Alkondi-Meybodi | 2011      | Yazd          | 0.03       |
| Farahmand       | 2012      | Tehran        | 0.00       |
| Bakhshipour     | 2012      | Zahedan       | 0.05       |
| Emami           | 2012      | Isfahan       | 0.04       |
| Mehrdad         | 2012      | Rasht         | 0.00       |
| Bakhshipour     | 2013      | Zahedan       | 0.03       |
| Amini-Ranjbar   | 2013      | Kerman        | 0.08       |
| Dehghani        | 2013      | Shiraz        | 0.01       |
| Househyar       | 2013      | Ardalib       | 0.10       |
| Shaykhiemani    | 2013      | Sanandaj      | 0.07       |
| Gheghhechichi1  | 2013      | Tabriz        | 0.08       |
| Shavayeste      | 2014      | Ahvaz         | 0.03       |
| Najafi          | 2014      | Tehran        | 0.03       |
| Yazdambod       | 2014      | Ardalib       | 0.01       |
| Honar           | 2015      | Shiraz        | 0.05       |
| Fallahi         | 2015      | Tehran        | 0.08       |
| Ahmadi          | 2015      | Kerman        | 0.03       |
| Dehghani        | 2015      | Shiraz        | 0.02       |

Overall (I-squared = 87.7%, p = 0.000)

Figure 3. Forest plot of prevalence of celiac disease used biopsy method
3.8. Publication of year studies included and prevalence of celiac disease
The prevalence of celiac disease in studies that had used serological tests for diagnosis and published in the years 2003-2007 was observed as 1% (95% CI: 0.01-0.02) in the years 2007-2011, 3% (95% CI: 0.02-0.04) for the years 2011-2015 and 4% (95% CI: 0.03-0.05) in the years 2011-2015. The prevalence of celiac disease in studies that had used the duodenal biopsy for diagnosis and published was 1% (95% CI: 0.01-0.01) in 2003-2007, 2% (95% CI: 0.01-0.02) for the years 2007 to 2011, and 3% (95% CI: 0.02-0.04) for the years 2011-2015.

Table 2. Results of subgroup analysis

| Variables             | Serological tests | Marsh |
|-----------------------|-------------------|-------|
|                       | Prevalence        | 95% CI| p-value | I2 (%)| Prevalence  | 95% CI| p-value | I2 (%)|
| <10                   | 3%                | 1%-4% | 0.000  | 60.5  | 2%          | 0%-4% | 0.012  | 74.4  |
| 10-20                 | 5%                | 3%-6% | 0.000  | 86.4  | 3%          | 1%-4% | 0.000  | 87.2  |
| 20-30                 | 3%                | 2%-4% | 0.000  | 93.0  | 1%          | 1%-2% | 0.000  | 0.0   |
| 30-40                 | 3%                | 3%-4% | 0.000  | 91.7  | 2%          | 2%-3% | 0.000  | 90.3  |
| 40-50                 | 2%                | 1%-4% | 0.003  | 95.8  | 0%          | 0%-1% | 0.003  | 0.0   |
| 50-60                 | 4%                | 0%-4% | 0.041  | -     | 1%          | -     | 0.315  | -     |
| Sample size           | <800              | 4%    | 3%-5%  | 0.000  | 85.7   | 3%    | 3%-4%  | 0.000  | 82.0   |
|                       | 800-1600          | 3%    | 2%-4%  | 0.000  | 96.0   | 0%    | 0%-1%  | 0.002  | 73.3   |
|                       | 1600-2400         | 2%    | -1%-6% | 0.191  | 98.5   | 1%    | 0%-1%  | 0.001  | -      |
|                       | >2400             | 1%    | 0%-2%  | 0.008  | 93.0   | 1%    | 1%-2%  | 0.000  | 71.0   |
| Quality of the studies| High              | 3%    | 2%-4%  | 0.000  | 91.3   | 3%    | 2%-3%  | 0.000  | 90.0   |
|                       | intermediate      | 5%    | 4%-7%  | 0.000  | 88.1   | 1%    | 1%-1%  | 0.000  | 85.8   |
|                       | Low               | 2%    | 1%-2%  | 0.000  | 88.1   | 4%    | 2%-6%  | 0.000  | 83.5   |
| Year of publication   | 2003-2007         | 1%    | 1%-2%  | 0.000  | 81.8   | 1%    | 1%-1%  | 0.000  | 73.9   |
|                       | 2007-2011         | 3%    | 2%-4%  | 0.000  | 90.0   | 2%    | 1%-2%  | 0.000  | 91.5   |
|                       | 2011-2015         | 4%    | 3%-5%  | 0.000  | 81.8   | 3%    | 2%-4%  | 0.000  | 73.9   |
| Regional background   | Central           | 3%    | 2%-4%  | 0.000  | 88.3   | 2%    | 2%-3%  | 0.000  | 81.8   |
|                       | North             | 1%    | 0%-1%  | 0.001  | 76.1   | 1%    | 0%-1%  | 0.004  | 46.0   |
|                       | South             | 2%    | 1%-3%  | 0.000  | 84.3   | 1%    | 0%-1%  | 0.003  | 83.8   |
|                       | West              | 5%    | 4%-7%  | 0.000  | 89.9   | 5%    | 3%-8%  | 0.000  | 85.0   |
|                       | East              | 4%    | 2%-5%  | 0.000  | 94.9   | 2%    | 1%-3%  | 0.000  | 91.0   |

3.9. Geographical background and prevalence of celiac disease
The prevalence of celiac disease was 3% (95% CI: 0.02-0.04) in studies that had used serological tests for the diagnosis and were carried out in central Iran, 1% (95% CI: 0.00-0.01) for studies conducted in northern Iran, 2% (95% CI: 0.01-0.03) for studies conducted in the south, 5% (95% CI: 0.0-0.07) for studies conducted in West region of Iran and 4% (95% CI: 0.02-0.05) for studies conducted in eastern regions. The prevalence of celiac disease was 2% (95% CI: 0.01-0.03) in studies that had used the duodenal biopsy for diagnosis, 1% (95% CI: 0.00-0.01) for studies conducted in central Iran, 1% (95% CI: 0.00-0.01) for studies carried out in northern Iran, 1% (95% CI: 0.00-0.01) for studies conducted in the south, 5% (95% CI: 0.03-0.08) for studies conducted in West region and 2% (95% CI: 0.01-0.03) for studies performed in the eastern regions.

3.10. Publication bias
The results of the assessment of publication bias were observed in the studies that had used serological tests for the diagnosis, and were observed for the tests Begg = 0.000, Egger = 0.000, and for studies that had used duodenal biopsy for the diagnosis, Begg = 0.001, Egger = 0.000. The results suggest that publication bias has occurred.

3.11. Sensitivity analysis
To ensure strong results, we excluded Mirzaagha’s study and conducted sensitivity analysis. For studies that had used serological tests, the prevalence remained unchanged and only CI 95%, 3% (95% CI: 0.03-0.04) changed. For studies that had used the duodenal biopsy, no change was created in prevalence. Hence exclusion of this study did not have much effect on the results.

3.12. Results of meta-regression
Meta-regression results are shown in Table (3). Meta-regression for studies that had used serological tests showed that the prevalence of celiac disease increases based on the publishing year of studies, decreases based on...
participants’ age, and increases based on a sample size of studies. But none are statistically significant. Meta-regression for studies that had used the duodenal biopsy, reduced based on the participants, age, and none were significant, but significantly increased based on sample size.

### Table 3. Results meta-regression analysis

| Items       | Serological tests | Marsh                      |
|-------------|-------------------|----------------------------|
|             | Coefficient | SE | T | p | 95% CI | Coefficient | SE | T | p | 95% CI |
| Year        | -0.00       | -0.11 | 0.34 | 0.95 | 0.00 | 0.00 | 0.00 | 0.00 | 0.60 | 0.55 | -0.00 | 0.00 |
| Age         | -0.00       | -0.00 | 0.86 | 0.17 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.20 | 0.83 | -0.00 | 0.00 |
| Sample size | -2.28       | -0.00 | 0.02 | -2.36 | -6.41 | 0.00 | 0.00 | 0.00 | 0.00 | 2.90 | -4.38 | -0.00 | -4.38 |
| Cons        | 3.01        | -8.25 | 0.35 | -0.93 | 2.81 | -2.62 | -1.35 | 2.32 | -0.58 | -0.56 | -6.05 | 3.35 |

### 3.13. Results of cumulative meta-analysis

For cumulative meta-analysis, studies and samples were ranked according to year of publication. Prevalence was declining for studies that used serological tests, when they were ranked according to year of publication and sample size. For studies that used duodenal biopsy, a decreasing prevalence was observed when studies were ranked according to year of publication and sample size.

### 4. Discussion

This study is the first systematic review and meta-analysis of celiac disease in Iran. The prevalence of celiac disease in different parts of Iran was studied. The results showed that the prevalence was 3% (95% CI: 0.03 - 0.03) for studies which used serological methods for diagnosis and 2% (95% CI: 0.01 - 0.02), for those used biopsy method for diagnosis. The prevalence of celiac disease was 0.71% in a study carried out in America (90) based on serological tests and 1.5% in Finland on the basis of conducted serological tests (91). In another study in Saudi Arabia (92), the prevalence rate was 3% and 1% respectively on the basis of serological tests and biopsy method. The results show that the prevalence of celiac disease in Iran is more than in developed countries and is almost identical to the developing countries. Differences in the prevalence difference, between developed and developing countries, may be due to ideal health status, better servicing, and more advanced medical equipment in developed countries. The difference observed between the prevalence of serological tests and a biopsy method in the present study, is often due to lack of proper and accurate use of biopsy for the diagnosis of celiac disease in the developing countries (93).

Unfortunately, in many cases, the diagnosis of celiac disease is solely based on serological tests. Factors such as intestinal parasitic and bacterial infections and malnutrition can cause changes in intestinal tissue similar to celiac disease characteristics. This could be the reason for the high prevalence of celiac disease in studies that have used serological tests. Our results showed that the lack of cohesion in the diagnostic criteria for celiac disease could be one reason for heterogeneity among studies based on p-value of Chi-square Test and I2. Additionally, high heterogeneity observed in this study may be due to the high number of studies and their sample size. Dietary habits can play an important role in the increased prevalence of celiac disease in respective countries. In the Iranian people's diet, grain and especially "Wheat", is widely consumed and this is an important factor for the increase in celiac disease. Celiac disease is rising not only in developed countries but in developing regions such as the Middle East, South Asia, North East, West Africa, and South America where taking a diet of grains, especially wheat, is common (94). Serologic tests are required in Iran for screening groups at risk to identify the disease. The prevalence of celiac disease is in all age groups up to 20 years. Given that traditional methods for breastfeeding and prolonged feeding with this practice and not cutting it at the right time is responsible for mild symptoms in these patients, these eating habits create a protecting effect for gluten intolerance in these individuals and a factor for more difficult reorganization of celiac disease (95). According to the study results, the prevalence of celiac disease is more common in the central and western regions of Iran. The high prevalence of celiac disease in these areas is because of the great city of Tehran. High population density, wrong eating habits, different ethnicities, population access to diagnostic centers of this disease can cause high prevalence in central Iran. Moreover, the prevalence of celiac disease is very high in Western Iran. Wheat consumption in these areas is very high. In the present study, some limitations were observed which can be referred as follows: 1) High heterogeneity was observed due to variety of diagnostic methods of patients in studies, this factor can influence the results, 2) The studies data were not possible for investigating the prevalence of celiac disease in terms of gender, 3) Only 36.9% of studies were of high-quality, which can be a cause for bias, 4) In some studies, only a diagnostic method had been used, 5) Carrying a large number of studies in Tehran also could be a factor affecting the bias, 6) The various diseases in people in some studies could also be another factor to influence the results. In conclusion, data from our meta-analysis confirmed
higher serological tests for the diagnosis compared to biopsy method for diagnosis celiac disease. Further studies regarding the entire Iranian population and compared serological tests and biopsy method are needed to validate diagnosis celiac disease.

5. Conclusions
In conclusion, celiac disease in Iran has an estimated prevalence that was 3% (95% CI: 0.03-0.03) for studies which used serological methods for diagnosis and 2% (95% CI: 0.01 - 0.02) for those which used biopsy method for diagnosis. The prevalence of celiac disease in Iran was similar or even higher than that reported world-wide.

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Conflict of Interest:
There is no conflict of interest to be declared.

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All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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