Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis

Prashant Singh,* Ananya Arora,† Tor A. Strand,§‖, Daniel A. Leffler,* Carlo Catassi,# Peter H. Green,**‡‡, Ciaran P. Kelly,* Vineet Ahuja,§§ and Govind K. Makharia§§

*Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; †Lady Hardinge Medical College, New Delhi, India; §Innlandet Hospital Trust, Lillehammer, Norway; ††Centre for International Health, University of Bergen, Bergen, Norway; ‡Gastroenterology Research and Development, Takeda Pharmaceuticals Inc, Cambridge, MA; #Department of Pediatrics, Università Politecnica delle Marche, Ancona, Italy; **Department of Medicine, ‡‡USA Celiac Disease Center, Columbia University Medical Center, New York, New York; §§Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, New Delhi, India

BACKGROUND & AIMS:
Celiac disease is a major public health problem worldwide. Although initially it was reported from countries with predominant Caucasian populations, it now has been reported from other parts of the world. The exact global prevalence of celiac disease is not known. We conducted a systematic review and meta-analysis to estimate the global prevalence of celiac disease.

METHODS:
We searched Medline, PubMed, and EMBASE for the keywords celiac disease, celiac, celiac disease, tissue transglutaminase antibody, anti-endomysium antibody, endomysial antibody, and prevalence for studies published from January 1991 through March 2016. Each article was cross-referenced with the words Asia, Europe, Africa, South America, North America, and Australia. The diagnosis of celiac disease was based on European Society of Pediatric Gastroenterology, Hepatology, and Nutrition guidelines. Of 3843 articles, 96 articles were included in the final analysis.

RESULTS:
The pooled global prevalence of celiac disease was 1.4% (95% confidence interval, 1.1%–1.7%) in 275,818 individuals, based on positive results from tests for anti–tissue transglutaminase and/or anti-endomysial antibodies (called seroprevalence). The pooled global prevalence of biopsy-confirmed celiac disease was 0.7% (95% confidence interval, 0.5%–0.9%) in 138,792 individuals. The prevalence values for celiac disease were 0.4% in South America, 0.5% in Africa and North America, 0.6% in Asia, and 0.8% in Europe and Oceania; the prevalence was higher in female vs male individuals (0.6% vs 0.4%; P < .001). The prevalence of celiac disease was significantly greater in children than adults (0.9% vs 0.5%; P < .001).

CONCLUSIONS:
In a systematic review and meta-analysis, we found celiac disease to be reported worldwide. The prevalence of celiac disease based on serologic test results is 1.4% and based on biopsy results is 0.7%. The prevalence of celiac disease varies with sex, age, and location. There is a need for population-based prevalence studies in many countries.

Keywords: Epidemiology; Gluten; Diet; Autoimmune Disorder.

Celiac disease (CD) is an autoimmune enteropathy triggered by dietary gluten in genetically susceptible individuals. Until a few decades ago, CD was considered to be an uncommon disease affecting mainly children and limited to individuals of European ancestry. In the 1970s, the diagnosis of CD required a sequence of 3 small intestinal biopsies, but the current guidelines suggest that its diagnosis should be based on the combination of a positive celiac-specific serologic test and small intestinal biopsy specimens showing villous abnormalities. Simplification of the diagnostic criteria and widespread use of serologic tests have made it possible to estimate the true prevalence of CD in the general population. Over the past 2 decades, CD has emerged as a major public health problem. Initial prevalence studies in the general population came from European countries and it was estimated to affect approximately 1% of the European population. CD subsequently was reported from other parts of the world with predominant Caucasian

Abbreviations used in this paper: Ab, antibody; AEA, anti-endomysial antibody; AGA, antigliadin antibody; CE, celiac disease; CI, confidence interval; tTG, tissue transglutaminase.
populations such as North America, Australia, and Brazil.6-8 In the past few decades, population-based data on the prevalence of CD also have been reported from the Middle East, India, and so forth.9-11

The prevalence of CD-predisposing HLA haplotypes in the general population and per-capita wheat composition, the 2 primary determinants of CD prevalence, vary from one region to the other.12,13 However, it is unclear if there is any variation in the prevalence of CD in different parts of the world. Although most reviews on CD suggest that the global prevalence of CD is approximately 1%, there has been no meta-analysis on this topic.12 A systematic review of the global prevalence of CD by Biagi et al14 had several limitations including an incomplete review of the literature, a lack of assessment of the quality of studies, and a lack of assessment of the risk of bias or heterogeneity. A few other systematic reviews on this topic had similar limitations and the authors of these systematic reviews did not attempt to pool the data.15,16

We therefore conducted a systematic review and meta-analysis of the published studies on the prevalence of CD to estimate the pooled prevalence, and variation in the prevalence, of CD around the world.

Methods

We conducted an extensive search on Medline, PubMed, and EMBASE with the following medical subject heading terms and keywords “celiac disease,” “celia,” “coeliac disease,” “tissue transglutaminase antibody,” “anti-endomysium antibody,” “endomysial antibody,” and “prevalence.” Each one was cross-referenced with “Asia,” “Europe,” “Africa,” “South America,” “North America,” and “Australia.” Because the European Society of Gastroenterology, Hepatology and Nutrition released the first modern guidelines for diagnosis of CD in 1990, we considered the year 1990 as a dividing year for well-defined diagnostic criteria for CD and all relevant articles published from January 1991 to March 2016 were included in this meta-analysis.17 Studies published after January 1991, with inclusion of study population before January 1991, were excluded from this systematic review. The articles also were identified using a hand search of the references of the studies whose full texts were accessed. There were no language restrictions on the search. Abstracts that were not published as full texts were not included in the present study.

Two authors (P.S. and A.A.) performed the literature search, reviewed all the full texts, and individually decided whether the study should be included or not based on predefined inclusion and exclusion criteria. Disagreements between the 2 authors were resolved by discussion. In case of persistent disagreement, the senior author (G.K.M.) reviewed the study and made the final decision.

Seroprevalence of Celiac Disease

For the present study, seroprevalence of CD in the population was considered as subjects having a positive anti–tissue transglutaminase (tTG) antibody (Ab) and/or anti-endomysial antibodies (AEAs). Because antigliadin antibody (AGA) is no longer recommended in the diagnostic algorithm of CD, studies reporting AGA alone were not considered for the estimation of seroprevalence of CD in the present systematic review.3

Diagnosis of Celiac Disease

CD was diagnosed if any of the following criteria were present: a combination of at least 1 positive celiac-specific serologic test such as anti-tTG Ab, AEA, or AGA, and demonstration of histologic changes of modified Marsh grade 2 or more on the small intestinal biopsies; and in the absence of data on celiac-specific serology, a combination of the presence of histologic changes of modified Marsh grade 2 or more on small intestinal biopsies and demonstration of clinical and/or histologic improvement after initiation of a gluten-free diet.3

Inclusion Criteria

All of the studies reporting the prevalence of CD in the general population were screened. Studies were included if they reported anti-tTG Ab or AEA as the initial screening test. Studies in which individuals did not undergo a biopsy after positive serology were included to calculate the pooled seroprevalence of CD but not for the pooled prevalence of CD.

Exclusion Criteria

The exclusion criteria included the following: (1) studies in which only high-risk subjects such as those with type 1 diabetes mellitus underwent testing; (2) studies documenting the prevalence based on self-reporting, database, or hospital registries; (3) if multiple studies were performed on the same stored sera, only the latest study was included; and (4) studies using AGA as the first-line or the sole screening test were excluded because AGA is no longer recommended as a sole screening test for CD.3 However, if AGA was used in combination with either anti-tTG Ab or AEA on all the individuals enrolled in a study, then these studies were included.

Risk of Bias Estimation

The risk of bias was calculated using the risk of bias tool for prevalence studies developed by Hoy et al.18 Based on this tool, studies were assessed for external and internal validity using a 10-point checklist and...
grouped into a low, moderate, or high risk of bias. The studies with a score of less than 6 were considered to have a high risk of bias, 6 to 8 was considered a moderate risk of bias, and 9 to 10 was considered a low risk of bias. The study(s) with a high risk of bias were excluded from the present systematic review.

**Data Extraction**

Two investigators (P.S. and A.A.) extracted the relevant data independently and the conflicts were resolved by consensus. The following information was extracted from each study: first author, year of publication, study design, number of people screened, type of serology used, number of seropositive participants, participants who underwent small intestinal mucosal biopsies, and results of the biopsies.

**Pooled Prevalence of Celiac Disease**

For calculation of the pooled prevalence of CD, only studies in which 50% or more of seropositive individuals (those with a positive anti-tTG and/or AEA) underwent a biopsy were included. The cut-off value of 50% was chosen arbitrability because we believed that including the studies in which less than 50% of seropositive individuals underwent a biopsy would falsely lower the actual prevalence of biopsy-proven CD. The studies in which less than 50% of seropositive individuals underwent a biopsy were included for calculation of pooled seroprevalence only.

**Statistical Analysis**

The meta-analysis was performed in line with the recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines. We used the meta package in R, version 3.2.1 (www.r-project.org) using random-effects models. Prevalence and forest plots were generated using the metaprop command. The Freeman–Tukey double-arc sine transformation was used for variance stabilization of proportions. Heterogeneity between studies was expressed by the $I^2$ statistic and the Cochran Q test for heterogeneity. $I^2$ values of 0%, less than 25%, 25% to 49% and more than 50% denoted no, low, moderate, and high heterogeneity, respectively. Results were considered significant if the $P$ value was less than .05.

**Results**

Our search found a total of 3843 articles in the database (Supplementary Figure 1). Of them, 3674 articles were excluded based on the titles or abstracts. Finally, full texts of 169 articles were assessed. Sixty-four additional studies were excluded based on the inclusion and exclusion criteria. Nine more studies were excluded for several reasons detailed in Supplementary Figure 1. Ultimately, 96 studies were included in the present meta-analysis (Supplementary Figure 1).

**Seroprevalence of Celiac Disease**

Pooled global seroprevalence of celiac disease. All 96 studies were included for the calculation of the pooled seroprevalence of CD. Of 275,818 individuals, 5571 individuals were reported to be positive for anti-tTG Ab and/or AEA. Thus, the pooled global seroprevalence of CD in the general population was 1.4% (95% confidence interval [CI], 1.1%–1.7%) (Figure 1). The $I^2$ test for heterogeneity was 97.5%, indicating significant heterogeneity among the studies.

Pooled seroprevalence of celiac disease in different continents. Of 96 studies, 49 studies were from Europe, 20 were from Asia, 11 were from South America, 7 were from North America, 7 were from Africa, and 1 was from Australia and New Zealand each. The pooled seroprevalence ranged from 1.1% (95% CI, 0.4%–2.2%) in Africa to 1.8% (95% CI, 1%–2.9%) in Asia (Table 1). The $I^2$ test for heterogeneity ranged from 91% in North America to 99% in Asia.

Pooled Global Prevalence of Celiac Disease

Of 96 studies included in the calculation of pooled seroprevalence, 25 studies were excluded because intestinal mucosal biopsies were not performed. Another 17 studies were excluded because less than 50% of seropositive individuals underwent a biopsy. Finally, 57 studies were included in this part of the analysis.

The main characteristics of these 57 studies are described in Table 2. Pooled global prevalence of celiac disease. In these 57 studies, a total of 1372 of 138,792 individuals were diagnosed to have biopsy-confirmed CD (Table 2). Thus, the global pooled prevalence of biopsy-confirmed CD in the present meta-analysis was 0.7% (95% CI, 0.5%–0.9%) (Figure 2). The $I^2$ test for heterogeneity for this part of the analysis was 92.3%.

Pooled prevalence of celiac disease in different continents. Of the earlier-mentioned 57 studies, 33 studies were from Europe, 12 were from Asia, 5 were from South America, 4 were from Africa, 2 were from Oceania, and only 1 was from North America (Table 1). The pooled prevalence of biopsy-proven CD ranged from 0.5% (95% CI, 0.2%–0.9%) in Africa to 0.8% (95% CI, 0.6%–1.1%) in Europe.

Of 7 studies included in the calculation of seroprevalence from North America, biopsies were not performed in 4 studies. In 2 other studies only 22.6% and 26.9% seropositive individuals underwent a biopsy and thus could not be included in this part of the study. Of the 57 studies included in the calculation of pooled seroprevalence, 26 studies were excluded because intestinal mucosal biopsies were not performed. Another 17 studies were excluded because less than 50% of seropositive individuals underwent a biopsy. Finally, 14 studies were included in this part of the analysis.
The study from Cuba screened 200 individuals and found 1 seropositive individual who subsequently had villous atrophy. Therefore, only 1 study could be included from North America for deriving the pooled prevalence of biopsy-confirmed CD. The I² test for heterogeneity ranged from 61% in Asia to 94% in Europe.

Country-wise pooled seroprevalence and prevalence of celiac disease. We also calculated the pooled seroprevalence and prevalence of CD for individual countries if the data were available. The countries were stratified into 4 percentile groups (0–25th, 26th–50th, 51st–75th, and 76th–100th).

With regard to seroprevalence, Algeria, Czech Republic, India, Israel, Mexico, Malaysia, Saudi Arabia, Sweden, Portugal, and Turkey belonged to the 76th to 100th percentile (pooled country-wise prevalence, 2.1%–8.5%), whereas Estonia, Germany, Iceland, Lithuania, Poland, Republic of San Marino, Spain, and Switzerland belonged to the 0 to 25th percentile (pooled country-wise prevalence, 0.2%–0.8%) (Figure 3).

When we stratified countries into quintiles based on biopsy-proven CD, Argentina, Egypt, Hungary, Finland, India, New Zealand, and Sweden were in the 76th to 100th percentile (pooled country-wise prevalence, 0.9%–2.4%). Among the countries where data from biopsy-proven CD were available, Brazil, Germany, Republic of San Marino, Russia, and Tunisia were among the 0 to 25th percentile (pooled country-wise prevalence, 0.2%–0.4%) (Figure 4).

Gender-Based Difference in the Prevalence of Biopsy-Confirmed Celiac Disease

Only 33 studies reported separate pooled prevalence of biopsy-confirmed CD for males and females. Of 33,149 males and 27,371 females, 156 males (0.4%, 95% CI, 0.3%–0.5%) and 213 females (0.6%; 95% CI, 0.5%–0.8%) were found to have biopsy-confirmed CD (P < .001). The I² test for heterogeneity was reduced to 57.5% among females and 66.3% among males.

Difference in the Prevalence of Biopsy-Confirmed Celiac Disease in Children and Adults

Of 57 studies included in the calculation of the pooled prevalence of biopsy-confirmed CD, 43 studies reported a separate pooled prevalence for pediatric and adult CD patients. Of 33,149 males and 27,371 females, 156 males (0.4%, 95% CI, 0.3%–0.5%) and 213 females (0.6%; 95% CI, 0.5%–0.8%) were found to have biopsy-confirmed CD (P < .001).

A total of 276 of 40,076 screened adults had CD, providing a pooled prevalence of 0.5% (95% CI, 0.3%–0.8%). Of 65,957 screened children, 891 children had CD, with a pooled prevalence of 0.9% (95% CI, 0.6%–1.3), which was higher than that in adults (P < .001). The I² test for heterogeneity was reduced to 57.5% among females and 66.3% among males.

---

**Figure 1.** Forest plot of pooled global seroprevalence of celiac disease based on 96 studies using tTG and/or AEA.
Exploring Heterogeneity

To explore heterogeneity further, we also grouped the studies based on the proportion (50%–74.9%, 75%–99.9%, and 100%) of seropositive individuals who underwent duodenal biopsies. However, heterogeneity did not seem to vary based on the proportion of seropositive individuals undergoing biopsies (results shown in the Supplementary Materials and Methods section). In addition, studies were also grouped based on the risk of bias (low or moderate). This also did not explain the heterogeneity (results shown in the Supplementary Materials and Methods section). Furthermore, we grouped studies into 2 groups: truly population-based and those that were not (studies based on healthy blood donors, school children, and so forth). Heterogeneity was similar in these 2 groups (results shown in the Supplementary Materials and Methods section).

Prevalence Over Time

To assess if the prevalence of CD is increasing over time, we stratified the studies into 2 time periods: January 1991 to December 2000 and January 2001 onward (based on the actual study period). The studies that overlapped these 2 time periods were removed from the analysis. The pooled prevalence of CD during the duration from 1991 to 2000 was 0.6% (95% CI, 0.5%–0.7%). The I² test for heterogeneity was reduced significantly to 67% in this group. The pooled global prevalence of CD between January 2011 and March 2016 was 0.8% (95% CI, 0.5%–1%), suggesting an increase in the prevalence of CD over time. The heterogeneity for this group was 94%.

Discussion

The present meta-analysis showed that the pooled global seroprevalence of CD is 1.4% (95% CI, 1.1%–1.7%). The pooled global prevalence of biopsy-confirmed CD is 0.7% (95% CI, 0.5%–0.9%), with the highest prevalence in Europe (0.8%) and Oceania (0.8%), and the least prevalence in South America (0.4%). The present meta-analysis confirms that biopsy-confirmed CD is 1.5 times more common in females than in males, and approximately twice more common in children than in adults.

In our study, the pooled prevalence of biopsy-confirmed CD was 0.7% (95% CI, 0.5%–0.9%). This is slightly higher than that reported by Biagi et al.14 (0.58%) and likely is owing to more rigorous literature search, methodology, and detailed analysis in the present study. Of such a large pool of patients with CD globally, the majority of patients (83%–95%) in developed countries, and possibly even a higher number in developing countries, still remain undiagnosed.10,118
Table 2. Description of Studies Included in the Meta-analysis of Pooled Global Prevalence of Biopsy Proven CD

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of study</th>
<th>Country</th>
<th>Region</th>
<th>Population</th>
<th>Children/ adults/ both</th>
<th>Risk of bias</th>
<th>Bias Score</th>
<th>Sample size</th>
<th>Serology used</th>
<th>Seropositive Patients with CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mora et al111</td>
<td>2012-2009</td>
<td>Argentina</td>
<td>Greater Buenos Aires, Santa Fe, Córdoba, Salta, and City of Buenos Aires</td>
<td>Children attending clinic for surgical reasons</td>
<td>Children</td>
<td>Moderate</td>
<td>6</td>
<td>2219</td>
<td>tTG followed by AEA</td>
<td>29</td>
</tr>
<tr>
<td>Chin et al102</td>
<td>2009 1994-1995</td>
<td>Australia</td>
<td>Busselton</td>
<td>General population</td>
<td>Adults</td>
<td>Moderate</td>
<td>6</td>
<td>3011</td>
<td>tTG</td>
<td>47</td>
</tr>
<tr>
<td>Alencar et al103</td>
<td>2012 2003-2004</td>
<td>Brazil</td>
<td>City of Sao Paulo</td>
<td>Healthy blood donors</td>
<td>Adults</td>
<td>Moderate</td>
<td>7</td>
<td>4000</td>
<td>tTG and AEA</td>
<td>24</td>
</tr>
<tr>
<td>Almeida et al104</td>
<td>2012 Not given</td>
<td>Brazil</td>
<td>Brazilian Northeastern states of Bahia, Piaui, and Sergipe</td>
<td>Afro-derivation population</td>
<td>Both</td>
<td>Moderate</td>
<td>6</td>
<td>840</td>
<td>AEA</td>
<td>0</td>
</tr>
<tr>
<td>Pratesi et al105</td>
<td>2003 1998-2000</td>
<td>Brazil</td>
<td>-</td>
<td>Consecutive outpatient blood draws</td>
<td>Both</td>
<td>Moderate</td>
<td>7</td>
<td>4405</td>
<td>AEA and AGA in IgA deficient</td>
<td>16</td>
</tr>
<tr>
<td>Pereira et al106</td>
<td>2006 2001</td>
<td>Brazil</td>
<td>-</td>
<td>Healthy blood donors</td>
<td>Adults</td>
<td>Moderate</td>
<td>6</td>
<td>2086</td>
<td>tTG followed by AEA</td>
<td>6</td>
</tr>
<tr>
<td>Galván et al107</td>
<td>2009 2007</td>
<td>Cuba</td>
<td>-</td>
<td>General population</td>
<td>Both</td>
<td>Moderate</td>
<td>6</td>
<td>200</td>
<td>tTG</td>
<td>1</td>
</tr>
<tr>
<td>Abu-Zekry et al108</td>
<td>2008 2001-2004</td>
<td>Egypt</td>
<td>-</td>
<td>Outpatient general clinic because of conditions unrelated to CD</td>
<td>Children</td>
<td>Moderate</td>
<td>6</td>
<td>1500</td>
<td>tTG followed by AEA</td>
<td>24</td>
</tr>
<tr>
<td>Vilppula et al110</td>
<td>2008 2002</td>
<td>Finland</td>
<td>Paijat Haime Hospital District</td>
<td>General population</td>
<td>Adults</td>
<td>Moderate</td>
<td>8</td>
<td>2815</td>
<td>tTG followed by AEA</td>
<td>44</td>
</tr>
<tr>
<td>Kolho et al111</td>
<td>1998 1996</td>
<td>Finland</td>
<td>-</td>
<td>Personnel of hospitals</td>
<td>Unclear</td>
<td>Moderate</td>
<td>7</td>
<td>1070</td>
<td>AEA</td>
<td>11</td>
</tr>
<tr>
<td>Mäki et al112</td>
<td>2003 1994</td>
<td>Finland</td>
<td>Five municipalities in northern Finland</td>
<td>School children</td>
<td>Children</td>
<td>Moderate</td>
<td>8</td>
<td>3654</td>
<td>tTG and AEA</td>
<td>56</td>
</tr>
<tr>
<td>Mustalahti et al113</td>
<td>2010 2000-2001</td>
<td>Finland</td>
<td>Country wide</td>
<td>General population</td>
<td>Adults</td>
<td>Moderate</td>
<td>8</td>
<td>6403</td>
<td>tTG followed by AEA</td>
<td>123</td>
</tr>
<tr>
<td>Kratzer et al114</td>
<td>2013 2002</td>
<td>Germany</td>
<td>Leutkirch</td>
<td>General population</td>
<td>Adults</td>
<td>Moderate</td>
<td>8</td>
<td>2157</td>
<td>tTG</td>
<td>14</td>
</tr>
<tr>
<td>Karagiozoglou- Lampoudi et al115</td>
<td>2013 After 2009</td>
<td>Greece</td>
<td>Thessaloniki, Heraklion, and Agrinio</td>
<td>Preschool children</td>
<td>Children</td>
<td>Low</td>
<td>9</td>
<td>1080</td>
<td>Biocard (Ani Biotech Oy, Vantaa, Finland) followed by tTG and AEA</td>
<td>8</td>
</tr>
<tr>
<td>Karponay Szabó et al116</td>
<td>1999 Not given</td>
<td>Hungary</td>
<td>Central district of Budapest</td>
<td>Preschool children</td>
<td>Children</td>
<td>Moderate</td>
<td>6</td>
<td>427</td>
<td>AEA</td>
<td>6</td>
</tr>
<tr>
<td>Karponay Szabó et al117</td>
<td>2007 2005</td>
<td>Hungary</td>
<td>Jász-Nagykun-Szolnok County</td>
<td>General population</td>
<td>Children</td>
<td>Low</td>
<td>9</td>
<td>2690</td>
<td>Biocard, AEA, and tTG</td>
<td>42</td>
</tr>
<tr>
<td>Johannsson et al118</td>
<td>2009 2004-2007</td>
<td>Iceland</td>
<td>Akureyri region</td>
<td>Healthy blood donors</td>
<td>Both</td>
<td>Moderate</td>
<td>6</td>
<td>813</td>
<td>tTG</td>
<td>6</td>
</tr>
<tr>
<td>Makharia et al119</td>
<td>2011 2008-2009</td>
<td>India</td>
<td>State of Haryana</td>
<td>General population</td>
<td>Both</td>
<td>Moderate</td>
<td>8</td>
<td>2879</td>
<td>tTG</td>
<td>50</td>
</tr>
<tr>
<td>Kochhar et al120</td>
<td>2012 2010-2011</td>
<td>India</td>
<td>-</td>
<td>Healthy blood donors</td>
<td>Adults</td>
<td>Moderate</td>
<td>7</td>
<td>1610</td>
<td>tTG</td>
<td>9</td>
</tr>
<tr>
<td>Dehghani et al121</td>
<td>2013 Not given</td>
<td>Iran</td>
<td>Shiraz city</td>
<td>School children</td>
<td>Children</td>
<td>Low</td>
<td>9</td>
<td>1500</td>
<td>tTG</td>
<td>30</td>
</tr>
<tr>
<td>Akbari et al122</td>
<td>2006 2003-2004</td>
<td>Iran</td>
<td>Cities of Sari and Kerman</td>
<td>General population</td>
<td>Adults</td>
<td>Low</td>
<td>9</td>
<td>2799</td>
<td>tTG and AEA</td>
<td>29</td>
</tr>
<tr>
<td>Study</td>
<td>Year(s)</td>
<td>Location/Country</td>
<td>Population Type</td>
<td>Category</td>
<td>Age</td>
<td>Prevalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------</td>
<td>---------------------------</td>
<td>--------------------------</td>
<td>-----------</td>
<td>-----</td>
<td>------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saberi-Firouzi et al</td>
<td>2008/2004</td>
<td>Iran, Shiraz city</td>
<td>General population</td>
<td>Adults</td>
<td>Low</td>
<td>1440</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bahari et al</td>
<td>2010/2006-07</td>
<td>Iran, Sistan and Baluchestan Province</td>
<td>Healthy blood donors</td>
<td>Adults</td>
<td>Moderate</td>
<td>1600</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farahmand et al</td>
<td>2012/2006-08</td>
<td>Iran, Tehran</td>
<td>School children</td>
<td>Children</td>
<td>Moderate</td>
<td>634</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israeli et al</td>
<td>2010/2003</td>
<td>Israel</td>
<td>Healthy military recruit</td>
<td>Adults</td>
<td>Moderate</td>
<td>850</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shamir et al</td>
<td>2002/2000-01</td>
<td>Israel</td>
<td>Healthy blood donors</td>
<td>Adults</td>
<td>Moderate</td>
<td>1571</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mustalahti et al</td>
<td>2010/1997-02</td>
<td>Italy, Alghero village</td>
<td>General population</td>
<td>Both</td>
<td>Moderate</td>
<td>7126</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bonamico et al</td>
<td>2011/2007</td>
<td>Italy</td>
<td>School children</td>
<td>Children</td>
<td>Moderate</td>
<td>4048</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volta et al</td>
<td>2001/1991-92</td>
<td>Italy</td>
<td>Towns of Campogalliano</td>
<td>Both</td>
<td>Low</td>
<td>3483</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carlsson et al</td>
<td>2001/1995-96</td>
<td>Italy, Malmo</td>
<td>General population</td>
<td>Children</td>
<td>Moderate</td>
<td>690</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catassi et al</td>
<td>2000/1997-98</td>
<td>Italy, Alghero area</td>
<td>General population</td>
<td>Children</td>
<td>Moderate</td>
<td>2096</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fabiani et al</td>
<td>2004/1999-01</td>
<td>Italy</td>
<td>General population</td>
<td>Both</td>
<td>Moderate</td>
<td>3541</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tommasini et al</td>
<td>2004/1999-00</td>
<td>Italy</td>
<td>School children</td>
<td>Children</td>
<td>Moderate</td>
<td>3188</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menardo et al</td>
<td>2006/2003</td>
<td>Italy</td>
<td>Village of Carcare in the hinterland of Liguria</td>
<td>Both</td>
<td>Moderate</td>
<td>1002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alarida et al</td>
<td>2011/Not given</td>
<td>Libya</td>
<td>City of El Beida</td>
<td>Children</td>
<td>Moderate</td>
<td>2920</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Csizmadia et al</td>
<td>1999/1997-98</td>
<td>The Netherlands</td>
<td>General population</td>
<td>Children</td>
<td>Low</td>
<td>6127</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rostami et al</td>
<td>1999/1997-98</td>
<td>The Netherlands</td>
<td>Healthy blood donors</td>
<td>Not given</td>
<td>Moderate</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cook et al</td>
<td>2000/1999</td>
<td>New Zealand</td>
<td>General population</td>
<td>Adults</td>
<td>Moderate</td>
<td>1064</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corazza et al</td>
<td>1997/Not given</td>
<td>Republic of San Marino</td>
<td>General population</td>
<td>Adults</td>
<td>Low</td>
<td>2237</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castaño et al</td>
<td>2004/2000-02</td>
<td>Spain</td>
<td>General population</td>
<td>Children</td>
<td>Moderate</td>
<td>484</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cilleruelo Pascua et al</td>
<td>2002/1999-00</td>
<td>Spain</td>
<td>Health district IX of Madrid</td>
<td>Children</td>
<td>Moderate</td>
<td>3378</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riestra et al</td>
<td>2000/1997-98</td>
<td>Spain</td>
<td>General population</td>
<td>Both</td>
<td>Low</td>
<td>1170</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garcia Novo et al</td>
<td>2007/2001-02</td>
<td>Spain</td>
<td>Healthy blood donors</td>
<td>Adults</td>
<td>Moderate</td>
<td>2215</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mariné et al</td>
<td>2010/2004-07</td>
<td>Spain</td>
<td>General population</td>
<td>Both</td>
<td>Low</td>
<td>4230</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year of study</td>
<td>Country</td>
<td>Region</td>
<td>Population</td>
<td>Children/adults/both</td>
<td>Risk of bias</td>
<td>Bias Score</td>
<td>Sample size</td>
<td>Serology used</td>
<td>Seropositive Patients with CD&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------</td>
<td>-----------------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>--------------------------</td>
<td>----------------------</td>
<td>--------------</td>
<td>------------</td>
<td>-------------</td>
<td>----------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Almazán et al&lt;sup&gt;93&lt;/sup&gt;</td>
<td>2015–2012</td>
<td>Spain</td>
<td>Maracena, in the metropolitan district of Granada, Spain</td>
<td>General population</td>
<td>Children</td>
<td>Low</td>
<td>9</td>
<td>198</td>
<td>POCT followed by tTG and AEA</td>
<td>6</td>
</tr>
<tr>
<td>Ivarsson et al&lt;sup&gt;90&lt;/sup&gt;</td>
<td>2013–2010</td>
<td>Sweden</td>
<td>-</td>
<td>School children</td>
<td>Children</td>
<td>Moderate</td>
<td>8</td>
<td>12,632</td>
<td>tTG</td>
<td>291</td>
</tr>
<tr>
<td>Myléus et al&lt;sup&gt;85&lt;/sup&gt;</td>
<td>2005–2006</td>
<td>Sweden</td>
<td>Cities and surrounding suburbs of Umea, Norrtalje, Norrköping, Växjö, and Lund</td>
<td>School children</td>
<td>Children</td>
<td>Low</td>
<td>9</td>
<td>7567</td>
<td>tTG</td>
<td>192</td>
</tr>
<tr>
<td>Ivarsson et al&lt;sup&gt;57&lt;/sup&gt;</td>
<td>1994</td>
<td>Sweden</td>
<td>Västerbotten and Norrbotten counties</td>
<td>General population</td>
<td>Adults</td>
<td>Low</td>
<td>9</td>
<td>1894</td>
<td>AGA and AEA</td>
<td>9</td>
</tr>
<tr>
<td>Rutz et al&lt;sup&gt;66&lt;/sup&gt;</td>
<td>1999–2000</td>
<td>Switzerland</td>
<td>The Canton of St. Gallen</td>
<td>School children</td>
<td>Children</td>
<td>Moderate</td>
<td>7</td>
<td>1450</td>
<td>tTG and AEA</td>
<td>11</td>
</tr>
<tr>
<td>Hariz et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>2013–2009</td>
<td>Tunisia</td>
<td>Island of Djerba</td>
<td>School children</td>
<td>Children</td>
<td>Moderate</td>
<td>7</td>
<td>2064</td>
<td>Rapid tTG followed by tTG and AEA</td>
<td>7</td>
</tr>
<tr>
<td>Bdioui et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>2002–2004</td>
<td>Tunisia</td>
<td>-</td>
<td>Healthy blood donors</td>
<td>Adults</td>
<td>Moderate</td>
<td>6</td>
<td>1418</td>
<td>AEA followed by tTG</td>
<td>3</td>
</tr>
<tr>
<td>Gursoy et al&lt;sup&gt;36&lt;/sup&gt;</td>
<td>2005</td>
<td>Turkey</td>
<td>Central Anatolia region</td>
<td>Patients at tertiary care undergoing phlebotomy for symptoms other than CD</td>
<td>Adults</td>
<td>Moderate</td>
<td>7</td>
<td>906</td>
<td>tTG</td>
<td>48</td>
</tr>
<tr>
<td>Ertekin et al&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Not given</td>
<td>Turkey</td>
<td>City of Erzurum</td>
<td>School children</td>
<td>Children</td>
<td>Low</td>
<td>9</td>
<td>1263</td>
<td>tTG</td>
<td>11</td>
</tr>
<tr>
<td>Demirçekik et al&lt;sup&gt;40&lt;/sup&gt;</td>
<td>2002–2003</td>
<td>Turkey</td>
<td>-</td>
<td>Healthy and children with disorders other than celiac visiting outpatient clinic</td>
<td>Children</td>
<td>Moderate</td>
<td>6</td>
<td>1000</td>
<td>tTG followed by AEA</td>
<td>10</td>
</tr>
<tr>
<td>El-Hadi et al&lt;sup&gt;71&lt;/sup&gt;</td>
<td>2000–2002</td>
<td>United Kingdom</td>
<td>-</td>
<td>General Population</td>
<td>Not given</td>
<td>Moderate</td>
<td>7</td>
<td>1000</td>
<td>tTG followed by AEA</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>138,792</td>
<td>1817</td>
<td></td>
<td>1372</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AEA, anti-endomysial antibody; CD, celiac disease; POCT, point-of-care test; tTG, tissue transglutaminase.

<sup>a</sup>Parentheses represent prevalence of CD in individual study.
The prevalence of CD varies from 0.4% in South America to 0.8% in Europe and Oceania. The factors responsible for this difference likely are genetic (including HLA and non-HLA genes), and environmental including patterns of wheat consumption, age at wheat introduction, infant feeding practices, gastrointestinal infections, antibiotic and proton-pump inhibitor use, and caesarian section rates.  

The prevalence of CD in a few geographic regions warrants some discussion. Although 1.4% of the North American population were seropositive for CD in the present meta-analysis, the exact proportion of biopsy-confirmed CD could not be established, mostly because seropositive individuals did not undergo a biopsy at all or fewer than 50% underwent a biopsy.

The seroprevalence of CD was observed to be highest in Asia (1.8%) and lowest in Africa (1.1%). In Africa, the population prevalence of the HLA-DQ2 haplotype and wheat consumption are significantly lower in sub-Saharan Africa compared with Northern Africa. Thus, it is very likely that the majority of the sub-Saharan population is less susceptible to CD than in other parts
of Africa. The only study from sub-Saharan Africa was from Burkina-Faso, where 600 individuals from the general population were screened and none were found to be seropositive for CD. The studies from Africa are generally from the Northern parts of Africa and thus the data from this systematic review mainly represent the prevalence from this region of the continent.

In addition, of the world’s top 10 most populous countries, population-based prevalence data on CD are available only from 4 countries (India, United States, Brazil, and Russia). Population-based prevalence data from the other 6 most populous countries (China, Indonesia, Pakistan, Nigeria, Bangladesh, and Japan) are lacking, although CD has been reported in each of these countries except Nigeria. There is a need for well-designed, population-based studies from many parts of the world. With a population of 143 million, reports on the prevalence of CD from Russia are sparse. Two small studies from Russia have screened a total of 3728 individuals with a seroprevalence of 1.4%, a prevalence closer to that observed in other parts of the world. There is a possibility of a large burden of CD in Russia, which needs to be explored.

What explains the difference between the pooled global seroprevalence of CD (1.4%) and the pooled global prevalence of biopsy-confirmed CD (0.7%)? We only included studies if at least 50% of the seropositive individuals underwent a biopsy for the calculation of the prevalence of CD. Still, there was a wide variation in the rate of seropositive individuals who underwent a biopsy.
and it ranged from 51.2% to 100%. This could have led to an underestimation of actual CD prevalence. In addition, some of these seropositive individuals may have had a false-positive screening test.

We noted several limitations of the estimates. First, there was a lack of population-based prevalence data from many countries across the world, and many of the available studies suffered from limitations such as a lack of an adequate number of subjects, lack of data on sex and age, and nonrandom sampling of the population at large. Second, many studies have reported a prevalence of CD based on the serology alone and even if the biopsies were performed in seropositive individuals, only a small proportion underwent biopsies. We therefore included only those studies in which at least 50% of subjects had undergone biopsies for reporting the prevalence of biopsy-confirmed CD. Similarly, we have no data on seronegative CD from these studies and therefore the pooled prevalence of CD in the present meta-analysis could be an underestimate of the exact prevalence of CD.

In conclusion, CD is a global disease and the global seroprevalence and prevalence of CD are 1.4% and 0.7%, respectively. The prevalence of CD varies with sex, age, and geographic location. The prevalence of CD has increased over time from 0.6% in 1991 to 2000 to 0.8% between 2001 and 2016. There is a need for population-based prevalence studies in many countries to estimate the global burden of CD properly.

References


Reprint requests
Address requests for reprints to: Govind K. Makharia, MD, DM, DNB, MNAMS, Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India. e-mail: govindmakharia@aiims.edu; fax: (91) 11-26588091 or (91) 11-26588663.

Conflicts of interest
These authors disclose the following: Ciaran P. Kelly has acted as a scientific advisor to companies attempting to develop new management approaches for celiac disease including Celimmune, Cour Pharma, Immunogen X, and Takeda Pharmaceuticals, and also acts as the Principal Investigator on a research grant on celiac disease supported by Aptalis; Daniel Lefler is the medical director at Takeda Pharmaceuticals and has received research support/consultancy fees from Alba Therapeutics, Alvine Pharmaceuticals, INOVA Diagnostics, Genzyme, Coronado Biosciences, the Sidney Frank Foundation, and Pfizer; and Peter H. Green has received personal fees from ImmusanT outside of the submitted work. The remaining authors disclose no conflicts.
Supplementary Materials and Methods

Exploring Heterogeneity

Heterogeneity by proportion of seropositive individuals undergoing a biopsy. We grouped the studies based on the proportion (50%–74.9%, 75%–99.9%, and 100%) of seropositive individuals who underwent duodenal mucosal biopsies. The $I^2$ test for heterogeneity varied from 69% in the group with 100% of seropositive individuals undergoing a biopsy, to 95% in the group with 75% to 99.9% of seropositive individuals undergoing a biopsy, and 82% in the group with 50% to 74.9% of seropositive individuals undergoing a biopsy.

If we calculated biopsy-proven CD based on all the studies irrespective of the percentage of seropositive patients undergoing a biopsy, the pooled prevalence of CD was 0.6% (95% CI, 0.5%–0.8%). The $I^2$ heterogeneity for this analysis was 92.5% and thus does not explain the heterogeneity.

Heterogeneity by risk of bias. We also grouped the studies based on their risk of bias (low, moderate, or high). The $I^2$ test for heterogeneity was 94% for studies with a low risk of bias and 91% for studies with a moderate risk of bias. Studies with a high risk of bias were excluded from the meta-analysis.

Heterogeneity by type of population studied. Of 57 studies that were included in the calculation of biopsy-proven CD, 23 were truly population-based and the others were based on healthy blood donors, healthy volunteers at medical centers, and so forth. The pooled prevalence of CD in these 23 population-based studies was 0.7% (95% CI, 0.5%–1.1), with the $I^2$ test for heterogeneity being 94.8%. The pooled prevalence of CD in the remaining 34 studies was 0.6% (95% CI, 0.5%–0.8) and the $I^2$ test for heterogeneity for this group was 88.6%. Thus, the type of population also did not significantly explain the heterogeneity.
Supplementary Figure 1. Flow diagram of studies included in the present meta-analysis.