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SYSTEMATIC REVIEWS AND META-ANALYSES

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

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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.[1] Until a few decades ago, CD was considered to be an uncommon disease affecting mainly children and limited to individuals of European ancestry.[1] 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.[2,3] 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.[1]

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.[4,5] CD subsequently was reported from

Abbreviations used in this paper: Ab, antibody; AEA, anti-endomysial antibody; AGA, antigliadin antibody; CE, celiac disease; CI, confidence interval; tTG, tissue transglutaminase.

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other parts of world with predominant Caucasian 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 al[14] 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," "celiac," "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 predecided 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.[18] 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.[19] We used the meta package in R, version 3.2.1 (www.r-project.org) using random-effects models.[20] Prevalence and forest plots were generated using the metaprop command. The Freeman–Tukey double-arcsine transformation was used for variance stabilization of proportions.[21] 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.[4,5,22–28] Ultimately, 96 studies were included in the present meta-analysis (Supplementary Figure 1).[4,6,9–11,29–116]

Seroprevalence of Celiac Disease

Pooled global seroprevalence of celiac disease. All 96 studies were included for the calculation of the pooled seroprevalence of CD.[4,6,9–11,29–116] 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.[4,6,9–11,29–116] 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.[4,6,9–11,29–116] 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.[9–11,31,33,34,36–42,47,48,50,53–56,58–61,63,65,66,68,70,71,74,76,77,80,82–85,87–89,92,93,96,101–103,105,109–111,115,116] 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[11,31,33,34] to 0.8% (95% CI, 0.6%–1.1%) in Europe.[53–61,63,65,66,68,70,71,74,76,77,80,82–85,87–93,115,116]

Of 7 studies included in the calculation of seroprevalence from North America,[6,95–100] biopsies were not performed in 4 studies.[95,97,99,100] 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

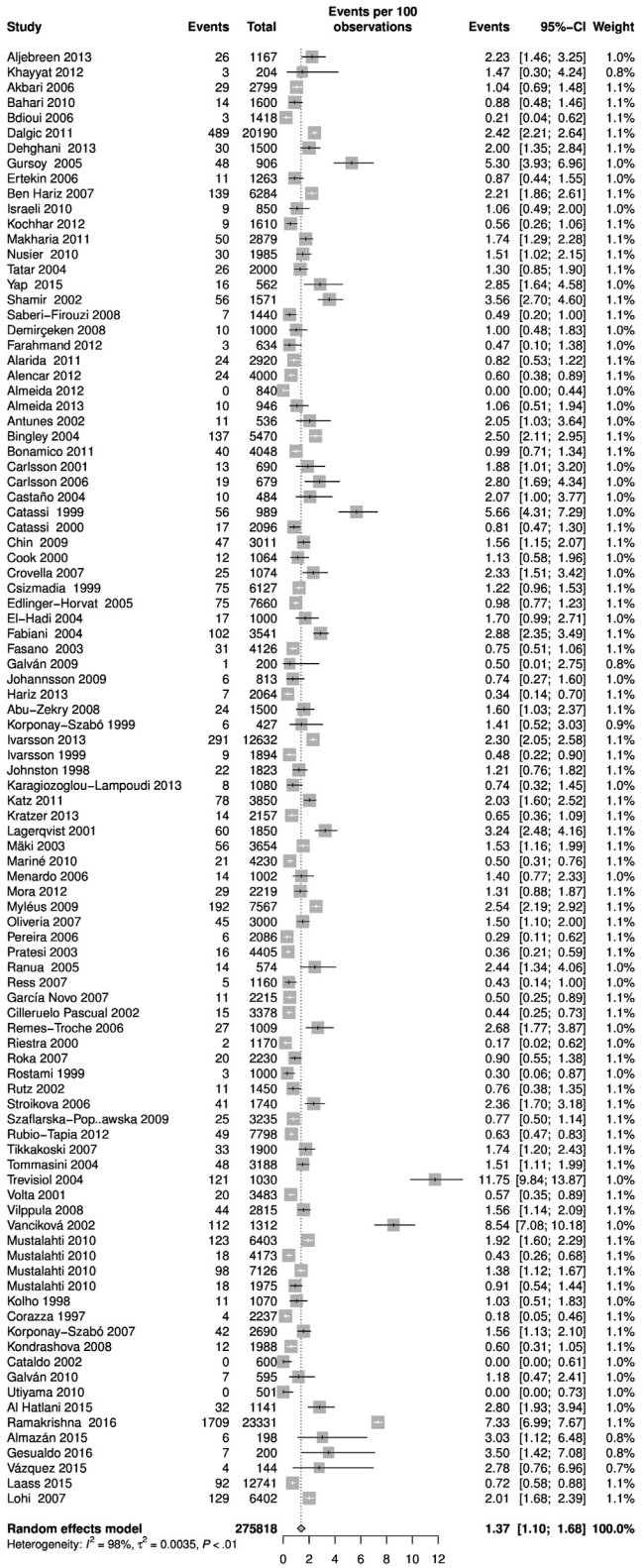

Figure 1. Forest plot of pooled global seroprevalence of celiac disease based on 96 studies using tTG and/or AEA.

analysis.[6,98] The study from Cuba screened 200 individuals and found 1 seropositive individual who subsequently had villous atrophy.[96] Therefore, only 1 study could be included from North America for deriving the pooled prevalence of biopsy-confirmed CD.[96] The I^2 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, Libya, 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 ($P < .001$).[9,10,31,33–35,37,38,41,47,48,50,56,57,59,60,63,66,74,76,82–84,87,91–93,96,101,103,105,106,109] The I^2 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.[10,11,31,33,34,36–42,47,48,50,53,56,57,59,61,65,66,68,70,76,77,80,82,83,85,88–93,101,102,105,109,111,116,117] 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 I^2 test for heterogeneity was 94% among children and 89% among adults.

Table 1. Pooled Seroprevalence and Prevalence of CD in Accordance With Geographic Location

Geographic location	Studies reporting seroprevalence, n	Population screened for seroprevalence	Subjects seropositive for CD	Pooled seroprevalence (95% CI)	Studies reporting prevalence of CD based on biopsy, n	Population screened for biopsy-proven CD	Subjects with biopsy-proven CD	Pooled prevalence of biopsy-proven CD (95% CI)
Continents								
Europe[a]	49	163,700	2340	1.3 (1.1–1.5)	33	98,391	1119	0.8 (0.6–1.1)
Asia	20	68,632	2607	1.8 (1–2.9)	12	18,052	114	0.6 (0.4–0.8)
South America	11	20,245	280	1.3 (0.5–2.5)	5	16,550	69	0.4 (0.1–0.6)
North America	7	17,778	200	1.4 (0.7–2.2)	1	200	01	0.5
Africa	7	15,775	253	1.1 (0.4–2.2)	4	7902	42	0.5 (0.2–0.9)
Oceania	2	4075	59	1.4 (1.1–1.8)	2	4075	27	0.8 (0.2–1.7)
Specific geographic regions								
Middle East[b]	17	41,750	847	1.6 (1.2–2.1)	11	15,063	89	0.6 (0.4–0.8)
South East Asia[c]	4	28,382	1784	2.6 (0.3–7.2)	2	4489	59	0.8 (0.4–1.4)
North Africa[d]	6	14,275	229	1.0 (0.2–2.3)	3	12,686	27	0.4 (0.2–0.6)

CD, celiac disease.
[a]Europe included data from Russia.
[b]Includes data from Iran, Turkey, Saudi Arabia, Israel, Jordan, and Egypt. All of these countries except Egypt have been included in Asia.
[c]Includes data from India and Malaysia. Data from both of these countries are included in Asia.
[d]Includes data from Tunisia, Libya, Algeria, and Burkina Faso. All of these countries along with Egypt constitute the data from Africa.

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%).[53–61,63,65,66,68,76,101–103,116] The I^2 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.[9,11,31,33,37,39–42,47,48,74,77,80,82,84,85,87,89–93,97,105,109,111] 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.[98,118]

Table 2. Description of Studies Included in the Meta-analysis of Pooled Global Prevalence of Biopsy Proven CD

Study	Year	Year of study	Country	Region	Population	Children/ adults/ both	Risk of bias	Bias Score	Sample size	Serology used	Seropositive	Patients with CD[a]
Mora et al[111]	2012	2008–2009	Argentina	Greater Buenos Aires, Santa Fe, Córdoba, Salta, and City of Buenos Aires	Children attending clinic for surgical reasons	Children	Moderate	6	2219	tTG followed by AEA	29	28 (1.26)
Chin et al[102]	2009	1994–1995	Australia	Busselton	General population	Adults	Moderate	6	3011	tTG	47	14 (0.46)
Alencar et al[109]	2012	2003–2004	Brazil	City of Sao Paulo	Healthy blood donors	Adults	Moderate	7	4000	tTG and AEA	24	14 (0.35)
Almeida et al[110]	2012	Not given	Brazil	Brazilian Northeastern states of Bahia, Piaui, and Sergpipe	Afro-derived population	Both	Moderate	6	840	AEA	0	0 (0)
Pratesi et al[103]	2003	1998–2000	Brazil	-	Consecutive outpatient blood draws	Both	Moderate	7	4405	AEA and AGA in IgA deficient	16	15 (0.34)
Pereira et al[105]	2006	2001	Brazil	-	Healthy blood donors	Adults	Moderate	6	2086	tTG followed by AEA	6	5 (0.24)
Galván et al[96]	2009	2007	Cuba	-	General population	Both	Moderate	6	200	tTG	1	1 (0.50)
Abu-Zekry et al[33]	2008	2001–2004	Egypt	-	Outpatient general clinic because of conditions unrelated to CD	Children	Moderate	6	1500	tTG followed by AEA	24	15 (1.00)
Ress et al[76]	2007	1998–1999	Estonia	Tartu County	School children	Children	Low	9	1160	tTG	5	4 (0.34)
Vilppula et al[82]	2008	2002	Finland	Paijat Haime Hospital District	General population	Adults	Moderate	8	2815	tTG followed by AEA	44	60 (2.13)
Kolho et al[54]	1998	1996	Finland	-	Personnel of hospitals	Unclear	Moderate	7	1070	AEA	11	8 (0.75)
Mäki et al[68]	2003	1994	Finland	Five municipalities in northern Finland	School children	Children	Moderate	8	3654	tTG and AEA	56	37 (1.01)
Mustalahti et al[88]	2010	2000–2001	Finland	Country wide	General population	Adults	Moderate	8	6403	tTG followed by AEA	123	85 (1.33)
Kratzer et al[92]	2013	2002	Germany	Leutkirch	General population	Adults	Moderate	8	2157	tTG	14	8 (0.37)
Karagiozoglou-Lampoudi et al[91]	2013	After 2009	Greece	Thessaloniki, Heraklion, and Agrinio	Preschool children	Children	Low	9	1080	Biocard (Ani Biotech Oy, Vantaa, Finland) followed by tTG and AEA	8	7 (0.65)
Karponay Szabó et al[56]	1999	Not given	Hungary	Central district of Budapest	Preschool children	Children	Moderate	6	427	AEA	6	5 (1.17)
Karponay Szabó et al[80]	2007	2005	Hungary	Jász-Nagykun-Szolnok County	General population	Children	Low	9	2690	Biocard, AEA, and tTG	42	37 (1.38)
Johannsson et al[84]	2009	2004–2007	Iceland	Akureyri region	Healthy blood donors	Both	Moderate	6	813	tTG	6	6 (0.74)
Makharia et al[9]	2011	2008–2009	India	State of Haryana	General population	Both	Moderate	8	2879	tTG	50	31 (1.08)
Kochhar et al[47]	2012	2010–2011	India	-	Healthy blood donors	Adults	Moderate	7	1610	tTG	9	9 (0.56)
Dehghani et al[50]	2013	Not given	Iran	Shiraz city	School children	Children	Low	9	1500	tTG	30	9 (0.60)
Akbari et al[37]	2006	2003–2004	Iran	Cities of Sari and Kerman	General population	Adults	Low	9	2799	tTG and AEA	29	9 (0.32)

Saberi-Firouzi et al[39]	2008	2004	Iran	Shiraz city	General population	Adults	Low	9	1440	tTG and AEA	7	2 (0.14)
Bahari et al[41]	2010	2006–2007	Iran	Sistan and Baluchestan Province	Healthy blood donors	Adults	Moderate	7	1600	tTG	14	7 (0.44)
Farahmand et al[48]	2012	2006–2008	Iran	Tehran	School children	Children	Moderate	8	634	tTG	3	3 (0.47)
Israeli et al[42]	2010	2003	Israel	-	Healthy military recruit	Adults	Moderate	7	850	tTG	9	6 (0.71)
Shamir et al[10]	2002	2000–2001	Israel	-	Healthy blood donors	Adults	Moderate	7	1571	tTG, AEA, AGA	56	10 (0.64)
Mustalahti et al[88]	2010	1997–2002	Italy	Alghero and village of Uri (Sassari) and village of Camerano (Ancona)	General population	Both	Moderate	8	7126	tTG followed by AEA	98	43 (0.60)
Bonamico et al[89]	2011	2007	Italy	7 municipalities of Rome	School children	Children	Moderate	7	4048	Salivary tTG followed by tTG and AEA	40	46 (1.14)
Volta et al[63]	2001	1991–1992	Italy	Towns of Campogalliano and Cormons	General population	Both	Low	9	3483	AEA	20	17 (0.49)
Carlsson et al[61]	2001	1995–1996	Italy	Malmo	General population	Children	Moderate	6	690	AEA	13	8 (1.16)
Catassi et al[59]	2000	1997–1998	Italy	Alghero area of northwest Sardinia	General population	Children	Moderate	8	2096	AEA	17	18 (0.86)
Fabiani et al[115]	2004	1999–2001	Italy	Camerano, Ancona (Marche region, middle Italy), and Alghero (Western Sardinia)	General population	Both	Moderate	7	3541	tTG followed by AEA	102	20 (0.56)
Tommasini et al[116]	2004	1999–2000	Italy	Trieste, northeast Italy	School children	Children	Moderate	7	3188	tTG followed by AEA	48	32 (1.00)
Menardo et al[74]	2006	2003	Italy	Village of Carcare in the hinterland of Liguria	General population	Both	Moderate	6	1002	tTG and AEA	14	10 (1.00)
Alarida et al[34]	2011	Not given	Libya	City of El Beida	School children	Children	Moderate	6	2920	tTG	24	20 (0.69)
Csizmadia et al[55]	1999	1997–1998	The Netherlands	Zuid Holland	General population	Children	Low	9	6127	AEA	75	31 (0.51)
Rostami et al[58]	1999	1997–1998	The Netherlands	-	Healthy blood donors	Not given	Moderate	6	1000	AEA	3	3 (0.30)
Cook et al[101]	2000	1999	New Zealand	Christchurch	General population	Adults	Moderate	8	1064	AEA	12	13 (1.22)
Corazza et al[53]	1997	Not given	Republic of San Marino	Country wide	General population	Adults	Low	10	2237	AEA	4	4 (0.18)
Kondrashova et al[83]	2008	1997–2001	Russia	Russian Karelia region	School children	Children	Moderate	7	1988	tTG followed by AEA	12	4 (0.20)
Castaño et al[70]	2004	2000–2002	Spain	County of Biscay	General population	Children	Moderate	7	484	tTG	10	7 (1.45)
Cilleruelo Pascua et al[65]	2002	1999–2000	Spain	Health district IX of Madrid	School children	Children	Moderate	7	3378	AEA and AGA if IgA deficient	17	21 (0.62)
Riestra et al[60]	2000	1997–1998	Spain	Langreo (Health Zone VIII of Asturias, northern Spain)	General population	Both	Low	10	1170	AEA	2	3 (0.26)
García Novo et al[77]	2007	2001–2002	Spain	Madrid	Healthy blood donors	Adults	Moderate	6	2215	tTG	11	6 (0.27)
Mariné et al[87]	2010	2004–2007	Spain	Region of Catalonia	General population	Both	Low	9	4230	tTG and AEA	21	21 (0.50)

Table 2. Continued

Study	Year	Year of study	Country	Region	Population	Children/ adults/ both	Risk of bias	Bias Score	Sample size	Serology used	Seropositive	Patients with CD[a]
Almazán et al[93]	2015	2009–2012	Spain	Maracena, in the metropolitan district of Granada, Spain	General population	Children	Low	9	198	POCT followed by tTG and AEA	6	6 (3.03)
Ivarsson et al[90]	2013	2005–2010	Sweden	-	School children	Children	Moderate	8	12,632	tTG	291	329 (2.60)
Myléus et al[85]	2009	2005–2006	Sweden	Cities and surrounding suburbs of Umea, Norrtalje, Norrkoping, Vaxjo, and Lund	School children	Children	Low	9	7567	tTG	192	195 (2.58)
Ivarsson et al[57]	1999	1994	Sweden	Västerbotten and Norrbotten counties	General population	Adults	Low	9	1894	AGA and AEA	9	10 (0.53)
Rutz et al[66]	2002	1999–2000	Switzerland	The Canton of St. Gallen	School children	Children	Moderate	7	1450	tTG and AEA	11	8 (0.55)
Hariz et al[11]	2013	2009	Tunisia	Island of Djerba	School children	Children	Moderate	7	2064	Rapid tTG followed by tTG and AEA	7	5 (0.24)
Bdioui et al[31]	2006	2002–2004	Tunisia	-	Healthy blood donors	Adults	Moderate	6	1418	AEA followed by tTG	3	2 (0.14)
Gursoy et al[36]	2005	Not given	Turkey	Central Anatolia region	Patients at tertiary care undergoing phlebotomy for symptoms other than CD	Adults	Moderate	7	906	tTG	48	12 (1.32)
Ertekin et al[38]	2006	Not given	Turkey	City of Erzurum	School children	Children	Low	9	1263	tTG	11	7 (0.55)
Demirçeken et al[40]	2008	2002–2003	Turkey	-	Healthy and children with disorders other than celiac visiting outpatient clinic	Children	Moderate	6	1000	tTG followed by AEA	10	9 (0.90)
El-Hadi et al[71]	2004	2000–2002	United Kingdom	-	General Population	Not given	Moderate	7	1000	tTG followed by AEA	17	6 (0.6)
Total									138,792		1817	1372

AEA, anti-endomysial antibody; CD, celiac disease; POCT, point-of-care test; tTG, tissue transglutaminase.
[a]Parentheses represent prevalence of CD in individual study.

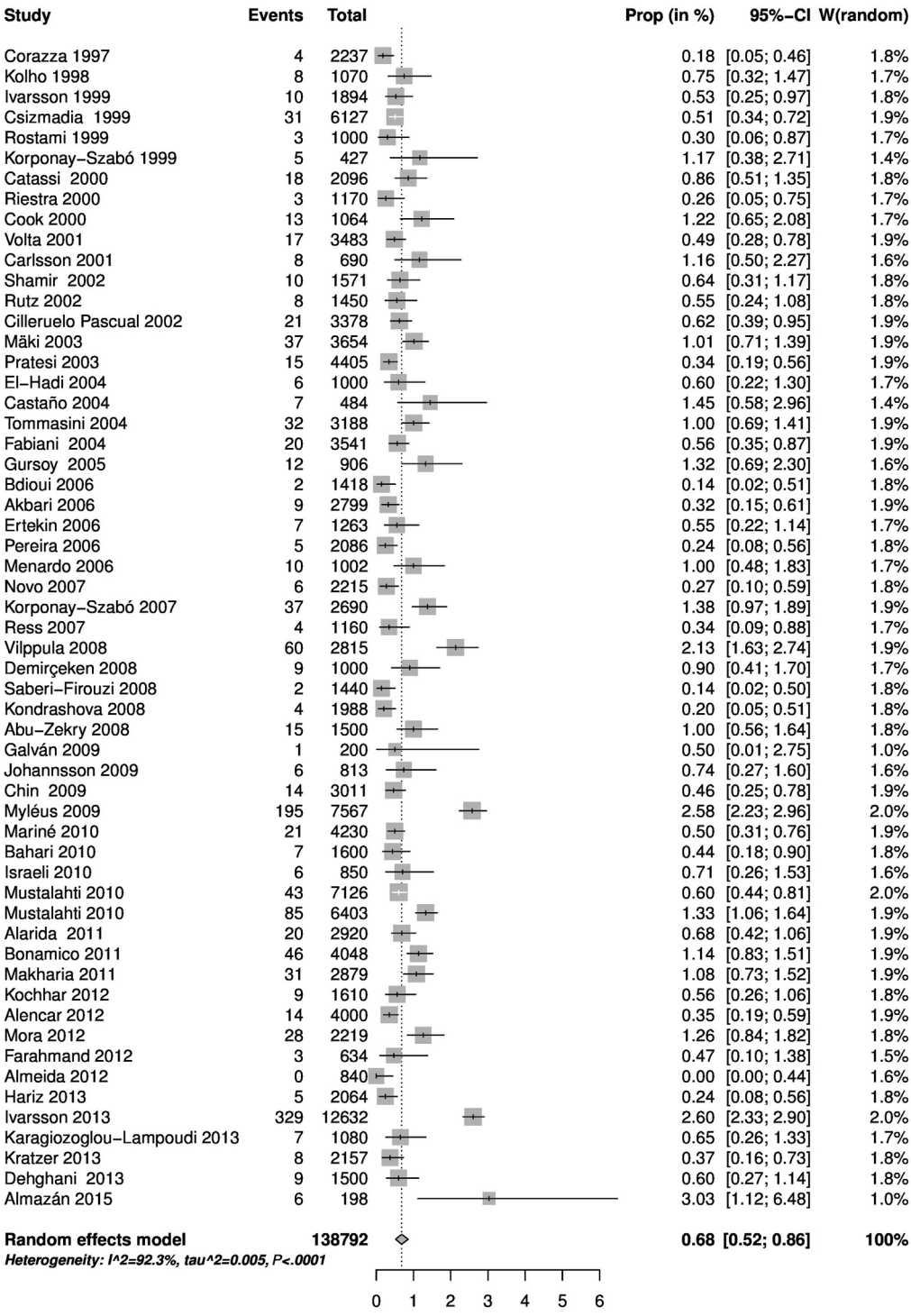

Figure 2. Forest plot of pooled global prevalence of biopsy-proven celiac disease based on 57 studies.

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.[119]

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.[120] Thus, it is very likely that the majority of the sub-Saharan population is less susceptible to CD than in other parts

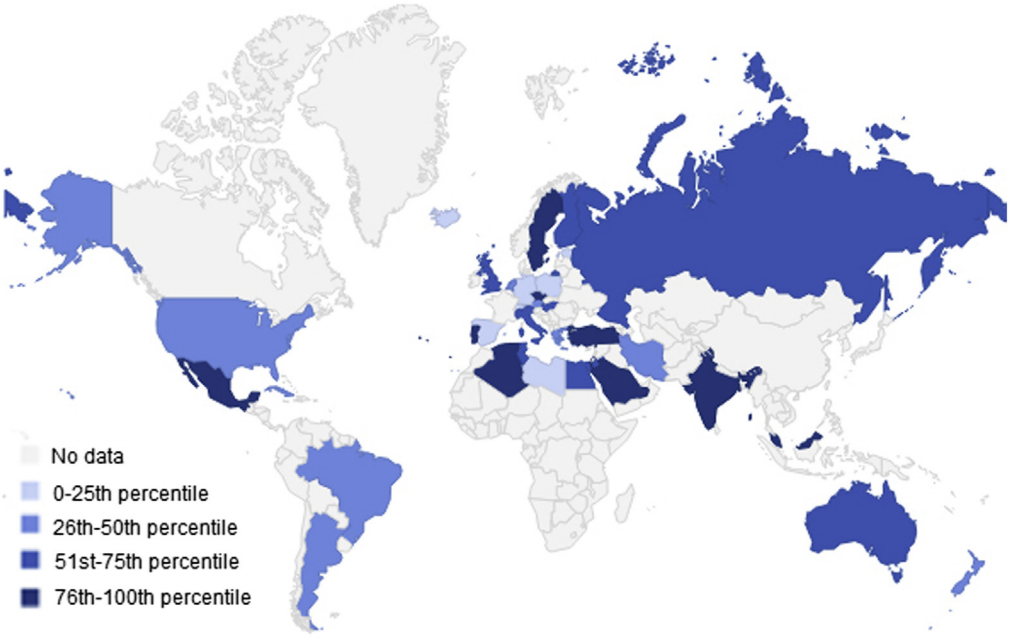

Figure 3. Worldwide celiac disease seroprevalence rates for the countries reporting data. Prevalence values were stratified into 4 groups of percentiles representing the 0 to 25th percentile (light gray) to the 76th to 100th percentile (dark black). The lowest and highest percentiles include countries with pooled national prevalence ranging from 0.2% to 0.8% and 2.1% to 8.5%, respectively.

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.[30] 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.[75,83] 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

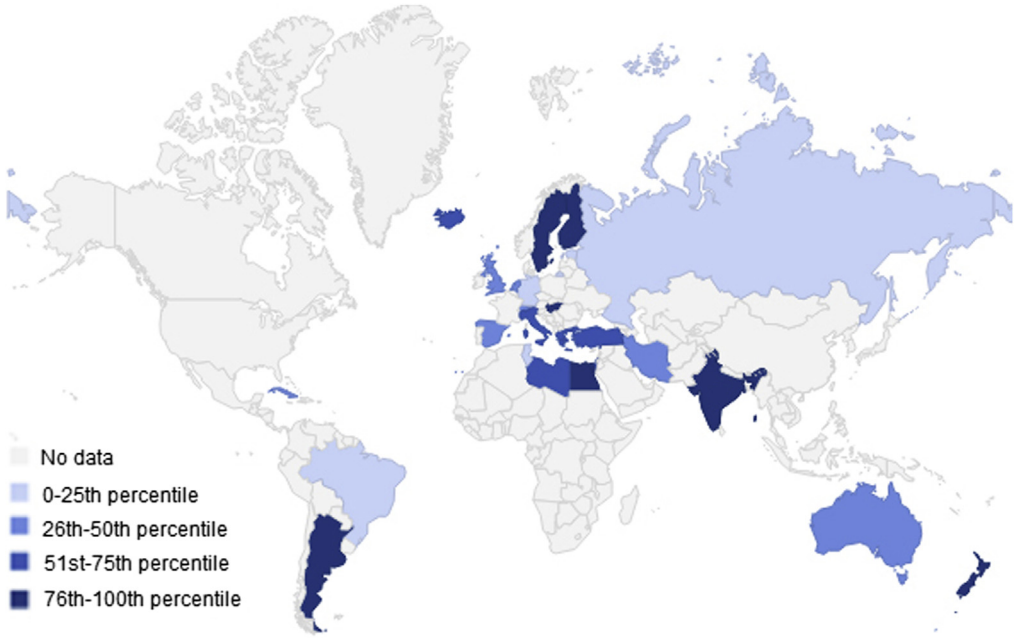

Figure 4. Worldwide celiac disease prevalence rates (based on biopsy) for the countries reporting data. Prevalence values were stratified into 4 groups of percentiles representing the 0 to 25th percentile (light gray) to the 76th to 100th percentile (dark black). The lowest and highest percentiles include countries with a pooled national prevalence ranging from 0.2% to 0.4% and 0.9% to 2.4%, respectively.

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.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2017.06.037.

References

1. Lionetti E, Catassi C. New clues in celiac disease epidemiology, pathogenesis, clinical manifestations, and treatment. Int Rev Immunol 2011;30:219–231.
2. Meeuwisse, GW. Diagnostic criteria in coeliac disease. Acta Paediatr Scand 1970;59:461–465.
3. Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012;54:136–160.
4. Johnston SD, Watson RG, McMillan SA, et al. Coeliac disease detected by screening is not silent–simply unrecognized. QJM 1998;91:853–860.
5. McMillan SA, Watson RP, McCrum EE, et al. Factors associated with serum antibodies to reticulin, endomysium, and gliadin in an adult population. Gut 1996;39:43–47.
6. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med 2003;163:286–292.
7. Hovell CJ, Collett JA, Vautier G, et al. High prevalence of coeliac disease in a population-based study from Western Australia: a case for screening? Med J Aust 2001;175:247–250.
8. Parra-Medina R, Molano-Gonzalez N, Rojas-Villarraga A, et al. Prevalence of celiac disease in Latin America: a systematic review and meta-regression. PLoS One 2015;10:e0124040.
9. Makharia GK, Verma AK, Amarchand R, et al. Prevalence of celiac disease in the northern part of India: a community based study. J Gastroenterol Hepatol 2011;26:894–900.
10. Shamir R, Lerner A, Shinar E, et al. The use of a single serological marker underestimates the prevalence of celiac disease in Israel: a study of blood donors. Am J Gastroenterol 2002; 97:2589–2594.
11. Hariz MB, Laadhar L, Kallel-Sellami M, et al. Celiac disease in Tunisian children: a second screening study using a "new generation" rapid test. Immunol Invest 2013;42:356–368.
12. Gujral N, Freeman HJ, Thomson AB. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. World J Gastroenterol 2012;18:6036–6059.
13. Cummins AG, Roberts-Thomson IC. Prevalence of celiac disease in the Asia-Pacific region. J Gastroenterol Hepatol 2009; 24:1347–1351.
14. Biagi F, Klersy C, Balduzzi D, et al. Are we not over-estimating the prevalence of coeliac disease in the general population? Ann Med 2010;42:557–561.
15. Kang JY, Kang AHY, Green A, et al. Systematic review: worldwide variation in the frequency of coeliac disease and changes over time. Aliment Pharmacol Ther 2013;38:226–245.
16. Dubé C, Rostom A, Sy R, et al. The prevalence of celiac disease in average-risk and at-risk Western European populations: a systematic review. Gastroenterology 2005;128:S57–S67.
17. Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. Arch Dis Child 1990;65:909–911.
18. Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol 2012;65:934–939.
19. Clarke M. The QUORUM statement. Lancet 2000;355:756–757.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.
21. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health 2014;72:39.
22. Challar MH, Jouma M, Sitzmann FC, et al. Prevalence of asymptomatic celiac disease in a Syrian population sample. JABMS 2004;6:155–160.
23. Dickey W, McMillan SA, McCrum EE, et al. Association between serum levels of total IgA and IgA class endomysial and antigliadin antibodies: implications for coeliac disease screening. Eur J Gastroenterol Hepatol 1997;9:559–562.
24. Borch K, Grodzinsky E, Petersson F, et al. Prevalence of coeliac disease and relations to Helicobacter pylori infection and duodenitis in a Swedish adult population sample: a histomorphological and serological survey. Inflammopharmacology 2000;8:341–350.
25. Trevisiol C, Not T, Berti I, et al. Screening for coeliac disease in healthy blood donors at two immuno-transfusion centres in north-east Italy. Ital J Gastroenterol Hepatol 1999;31:584–586.
26. Mazzetti di Pietralata M, Giorgetti GM, Gregori M, et al. Subclinical coeliac disease. Ital J Gastroenterol 1992;24:352–354.
27. Melo SBC, Fernandes MIM, Peres LC, et al. Prevalence and demographic characteristics of celiac disease among blood donors in Ribeirão Preto, State of São Paulo, Brazil. Dig Dis Sci 2006;51:1020–1025.

28. Schweizer JJ, Blomberg BME von, Bueno-de Mesquita HB, et al. Coeliac disease in The Netherlands. Scand J Gastroenterol 2004;39:359–364.
29. Catassi C, Rätsch IM, Gandolfi L, et al. Why is coeliac disease endemic in the people of the Sahara? Lancet 1999; 354:647–648.
30. Cataldo F, Lio D, Simpore J, et al. Consumption of wheat foodstuffs not a risk for celiac disease occurrence in Burkina Faso. J Pediatr Gastroenterol Nutr 2002;35:233–234.
31. Bdioui F, Sakly N, Hassine M, et al. Prevalence of celiac disease in Tunisian blood donors. Gastroenterol Clin Biol 2006;30:33–36.
32. Ben Hariz M, Kallel-Sellami M, Kallel L, et al. Prevalence of celiac disease in Tunisia: mass-screening study in school-children. Eur J Gastroenterol Hepatol 2007;19:687–694.
33. Abu-Zekry M, Kryszak D, Diab M, et al. Prevalence of celiac disease in Egyptian children disputes the east-west agriculture-dependent spread of the disease. J Pediatr Gastroenterol Nutr 2008;47:136–140.
34. Alarida K, Harown J, Ahmaida A, et al. Coeliac disease in Libyan children: a screening study based on the rapid determination of anti-transglutaminase antibodies. Dig Liver Dis 2011; 43:688–691.
35. Tatar G, Elsurer R, Simsek H, et al. Screening of tissue transglutaminase antibody in healthy blood donors for celiac disease screening in the Turkish population. Dig Dis Sci 2004; 49:1479–1484.
36. Gursoy S, Guven K, Simsek T, et al. The prevalence of unrecognized adult celiac disease in Central Anatolia. J Clin Gastroenterol 2005;39:508–511.
37. Akbari MR, Mohammadkhani A, Fakheri H, et al. Screening of the adult population in Iran for coeliac disease: comparison of the tissue-transglutaminase antibody and anti-endomysial antibody tests. Eur J Gastroenterol Hepatol 2006;18:1181–1186.
38. Ertekin V, Selimoğlu MA, Altnkaynak S. Prevalence of cyclic vomiting syndrome in a sample of Turkish school children in an urban area. J Clin Gastroenterol 2006;40:896–898.
39. Saberi-Firouzi M, Omrani GR, Nejabat M, et al. Prevalence of celiac disease in Shiraz, southern Iran. Saudi J Gastroenterol 2008;14:135–138.
40. Demirçeken FG, Kansu A, Kuloğlu Z, et al. Human tissue transglutaminase antibody screening by immunochromatographic line immunoassay for early diagnosis of celiac disease in Turkish children. Turk J Gastroenterol 2008;19:14–21.
41. Bahari A, Karimi M, Sanei-Moghaddam I, et al. Prevalence of celiac disease among blood donors in Sistan and Balouchestan Province, Southeastern Iran. Arch Iran Med 2010;13:301–305.
42. Israeli E, Hershcovici T, Grotto I, et al. Prevalence of celiac disease in an adult Jewish population in Israel. Isr Med Assoc J 2010;12:266–269.
43. Nusier MK, Brodtkorb HK, Rein SE, et al. Serological screening for celiac disease in schoolchildren in Jordan. Is height and weight affected when seropositive? Ital J Pediatr 2010;36:16.
44. Dalgic B, Sari S, Basturk B, et al. Prevalence of celiac disease in healthy Turkish school children. Am J Gastroenterol 2011; 106:1512–1517.
45. Ramakrishna BS, Makharia GK, Chetri K, et al. Prevalence of adult celiac disease in India: regional variations and associations. Am J Gastroenterol 2016;111:115–123.
46. Khayyat YM. Serologic markers of gluten sensitivity in a healthy population from the western region of Saudi Arabia. Saudi J Gastroenterol 2012;18:23–25.
47. Kochhar R, Sachdev S, Kochhar R, et al. Prevalence of coeliac disease in healthy blood donors: a study from north India. Dig Liver Dis 2012;44:530–532.
48. Farahmand F, Mir-Nasseri MM, Shahraki T, et al. Prevalence of occult celiac disease in healthy Iranian school age children. Arch Iran Med 2012;15:342–345.
49. Aljebreen AM, Almadi MA, Alhammad A, et al. Seroprevalence of celiac disease among healthy adolescents in Saudi Arabia. World J Gastroenterol 2013;19:2374–2378.
50. Dehghani SM, Haghighat M, Mobayen A, et al. Prevalence of celiac disease in healthy Iranian school children. Ann Saudi Med 2013;33:159–161.
51. Yap TW-C, Chan W-K, Leow AH-R, et al. Prevalence of serum celiac antibodies in a multiracial Asian population–a first study in the young Asian adult population of Malaysia. PLoS One 2015; 10:e0121908.
52. Al Hatlani MM. Prevalence of celiac disease among symptom-free children from the Eastern Province of Saudi Arabia. Saudi J Gastroenterol 2015;21:367–371.
53. Corazza GR, Andreani ML, Biagi F, et al. The smaller size of the "coeliac iceberg" in adults. Scand J Gastroenterol 1997; 32:917–919.
54. Kolho KL, Färkkilä MA, Savilahti E. Undiagnosed coeliac disease is common in Finnish adults. Scand J Gastroenterol 1998; 33:1280–1283.
55. Csizmadia CG, Mearin ML, Blomberg BM von, et al. An iceberg of childhood coeliac disease in the Netherlands. Lancet 1999; 353:813–814.
56. Korponay-Szabó IR, Kovács JB, Czinner A, et al. High prevalence of silent celiac disease in preschool children screened with IgA/IgG antiendomysium antibodies. J Pediatr Gastroenterol Nutr 1999;28:26–30.
57. Ivarsson A, Persson LA, Juto P, et al. High prevalence of undiagnosed coeliac disease in adults: a Swedish population-based study. J Intern Med 1999;245:63–68.
58. Rostami K, Mulder CJ, Werre JM, et al. High prevalence of celiac disease in apparently healthy blood donors suggests a high prevalence of undiagnosed celiac disease in the Dutch population. Scand J Gastroenterol 1999;34:276–279.
59. Catassi C, Fanciulli G, D'Appello AR, et al. Antiendomysium versus antigliadin antibodies in screening the general population for coeliac disease. Scand J Gastroenterol 2000; 35:732–736.
60. Riestra S, Fernández E, Rodrigo L, et al. Prevalence of coeliac disease in the general population of northern Spain. Strategies of serologic screening. Scand J Gastroenterol 2000;35:398–402.
61. Carlsson AK, Axelsson IE, Borulf SK, et al. Serological screening for celiac disease in healthy 2.5-year-old children in Sweden. Pediatrics 2001;107:42–45.
62. Lagerqvist C, Ivarsson A, Juto P, et al. Screening for adult coeliac disease - which serological marker(s) to use? J Intern Med 2001;250:241–248.
63. Volta U, Bellentani S, Bianchi FB, et al. High prevalence of celiac disease in Italian general population. Dig Dis Sci 2001; 46:1500–1505.
64. Antunes H. First study on the prevalence of celiac disease in a Portuguese population. J Pediatr Gastroenterol Nutr 2002; 34:240.
65. Cilleruelo Pascual ML, Román Riechmann E, Jiménez Jiménez J, et al. [Silent celiac disease: exploring the iceberg in the school-aged population]. An Esp Pediatr 2002;57:321–326.

66. Rutz R, Ritzler E, Fierz W, et al. Prevalence of asymptomatic celiac disease in adolescents of eastern Switzerland. Swiss Med Wkly 2002;132:43–47.
67. Vanciková Z, Chlumecký V, Sokol D, et al. The serologic screening for celiac disease in the general population (blood donors) and in some high-risk groups of adults (patients with autoimmune diseases, osteoporosis and infertility) in the Czech republic. Folia Microbiol (Praha) 2002;47:753–758.
68. Mäki M, Mustalahti K, Kokkonen J, et al. Prevalence of celiac disease among children in Finland. N Engl J Med 2003; 348:2517–2524.
69. Bingley PJ, Williams AJK, Norcross AJ, et al. Undiagnosed coeliac disease at age seven: population based prospective birth cohort study. BMJ 2004;328:322–323.
70. Castaño L, Blarduni E, Ortiz L, et al. Prospective population screening for celiac disease: high prevalence in the first 3 years of life. J Pediatr Gastroenterol Nutr 2004;39:80–84.
71. El-Hadi S, Tuthill D, Lewis E, et al. Unrecognised coeliac disease is common in healthcare students. Arch Dis Child 2004;89:842.
72. Ranua J, Luoma K, Auvinen A, et al. Celiac disease-related antibodies in an epilepsy cohort and matched reference population. Epilepsy Behav 2005;6:388–392.
73. Carlsson A, Agardh D, Borulf S, et al. Prevalence of celiac disease: before and after a national change in feeding recommendations. Scand J Gastroenterol 2006;41:553–558.
74. Menardo G, Brizzolara R, Bonassi S, et al. Population screening for coeliac disease in a low prevalence area in Italy. Scand J Gastroenterol 2006;41:1414–1420.
75. Stroikova M, Augul N, Gureev J, et al. Screening of blood donors for tissue transglutaminase antibodies in the Ryazan area (Russia). Dig Liver Dis 2006;38:617–619.
76. Ress K, Harro M, Maaroos H-I, et al. High prevalence of coeliac disease: need for increasing awareness among physicians. Dig Liver Dis 2007;39:136–139.
77. García Novo MD, Garfia C, Acuña Quirós MD, et al. [Prevalence of celiac disease in apparently healthy blood donors in the autonomous community of Madrid]. Rev Esp Enferm Dig 2007; 99:337–342.
78. Roka V, Potamianos SP, Kapsoritakis AN, et al. Prevalence of coeliac disease in the adult population of central Greece. Eur J Gastroenterol Hepatol 2007;19:982–987.
79. Tikkakoski S, Savilahti E, Kolho K-L. Undiagnosed coeliac disease and nutritional deficiencies in adults screened in primary health care. Scand J Gastroenterol 2007;42:60–65.
80. Korponay-Szabó IR, Szabados K, Pusztai J, et al. Population screening for coeliac disease in primary care by district nurses using a rapid antibody test: diagnostic accuracy and feasibility study. BMJ 2007;335:1244–1247.
81. Lohi S, Mustalahti K, Kaukinen K, et al. Increasing prevalence of coeliac disease over time. Aliment Pharmacol Ther 2007; 26:1217–1225.
82. Vilppula A, Collin P, Mäki M, et al. Undetected coeliac disease in the elderly: a biopsy-proven population-based study. Dig Liver Dis 2008;40:809–813.
83. Kondrashova A, Mustalahti K, Kaukinen K, et al. Lower economic status and inferior hygienic environment may protect against celiac disease. Ann Med 2008;40:223–231.
84. Johannsson GF, Kristjansson G, Cariglia N, et al. The prevalence of celiac disease in blood donors in Iceland. Dig Dis Sci 2009;54:348–350.
85. Myléus A, Ivarsson A, Webb C, et al. Celiac disease revealed in 3% of Swedish 12-year-olds born during an epidemic. J Pediatr Gastroenterol Nutr 2009;49:170–176.
86. Szaflarska-Popławska A, Parzecka M, Müller L, et al. Screening for celiac disease in Poland. Med Sci Monit 2009; 15:PH7–PH11.
87. Mariné M, Farre C, Alsina M, et al. The prevalence of coeliac disease is significantly higher in children compared with adults. Aliment Pharmacol Ther 2011;33:477–486.
88. Mustalahti K, Catassi C, Reunanen A, et al. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. Ann Med 2010;42:587–595.
89. Bonamico M, Nenna R, Montuori M, et al. First salivary screening of celiac disease by detection of anti-transglutaminase autoantibody radioimmunoassay in 5000 Italian primary schoolchildren. J Pediatr Gastroenterol Nutr 2011;52:17–20.
90. Ivarsson A, Myléus A, Norström F, et al. Prevalence of childhood celiac disease and changes in infant feeding. Pediatrics 2013; 131:e687–e694.
91. Karagiozoglou-Lampoudi T, Zellos A, Vlahavas G, et al. Screening for coeliac disease in preschool Greek children: the feasibility study of a community-based project. Acta Paediatr 2013;102:749–754.
92. Kratzer W, Kibele M, Akinli A, et al. Prevalence of celiac disease in Germany: a prospective follow-up study. World J Gastroenterol 2013;19:2612–2620.
93. Almazán MV, Ortega E, Moreno Torres R, et al. Diagnostic screening for subclinical celiac disease using a rapid test in children aged 2-4. Pediatr Res 2015;78:280–285.
94. Laass MW, Schmitz R, Uhlig HH, et al. The prevalence of celiac disease in children and adolescents in Germany. Dtsch Arztebl Int 2015;112:553–560.
95. Remes-Troche JM, Ramírez-Iglesias MT, Rubio-Tapia A, et al. Celiac disease could be a frequent disease in Mexico: prevalence of tissue transglutaminase antibody in healthy blood donors. J Clin Gastroenterol 2006;40:697–700.
96. Galván JA, Lemos G, Fernández de Cossio ME, et al. Silent celiac disease in a cohort of healthy adults. Autoimmunity 2009; 42:705–708.
97. Galvan JA. Screening for celiac disease in a healthy Cuban children cohort from Pinar del Río province. Biotecnol Apl 2010; 27:291–293.
98. Katz KD, Rashtak S, Lahr BD, et al. Screening for celiac disease in a North American population: sequential serology and gastrointestinal symptoms. Am J Gastroenterol 2011; 106:1333–1339.
99. Rubio-Tapia A, Ludvigsson JF, Brantner TL, et al. The prevalence of celiac disease in the United States. Am J Gastroenterol 2012;107:1538–1545.
100. Gesualdo PD, Bautista KA, Waugh KC, et al. Feasibility of screening for T1D and celiac disease in a pediatric clinic setting. Pediatr Diabetes 2016;17:441–448.
101. Cook HB, Burt MJ, Collett JA, et al. Adult coeliac disease: prevalence and clinical significance. J Gastroenterol Hepatol 2000;15:1032–1036.
102. Chin MW, Mallon DF, Cullen DJ, et al. Screening for coeliac disease using anti-tissue transglutaminase antibody assays, and prevalence of the disease in an Australian community. Med J Aust 2009;190:429–432.

103. Pratesi R, Gandolfi L, Garcia SG, et al. Prevalence of coeliac disease: unexplained age-related variation in the same population. Scand J Gastroenterol 2003;38:747–750.
104. Trevisiol C, Brandt KG, Silva GAP, et al. High prevalence of unrecognized celiac disease in an unselected hospital population in north-eastern Brasil (Recife, Pernambuco). J Pediatr Gastroenterol Nutr 2004;39:214–215.
105. Pereira MAG, Ortiz-Agostinho CL, Nishitokukado I, et al. Prevalence of celiac disease in an urban area of Brazil with predominantly European ancestry. World J Gastroenterol 2006; 12:6546–6550.
106. Crovella S, Brandao L, Guimaraes R, et al. Speeding up coeliac disease diagnosis in the developing countries. Dig Liver Dis 2007;39:900–902.
107. Oliveira RP, Sdepanian VL, Barreto JA, et al. High prevalence of celiac disease in Brazilian blood donor volunteers based on screening by IgA antitissue transglutaminase antibody. Eur J Gastroenterol Hepatol 2007;19:43–49.
108. Utiyama SR da R, Ribas JLC, Nisihara RM, et al. Celiac disease in native Indians from Brazil: a clinical and epidemiological survey. North Am J Med Sci 2010;2:138–142.
109. Alencar ML, Ortiz-Agostinho CL, Nishitokukado L, et al. Prevalence of celiac disease among blood donors in São Paulo: the most populated city in Brazil. Clinics (São Paulo) 2012; 67:1013–1018.
110. Almeida RC, Gandolfi L, De Nazaré Klautau-Guimarães M, et al. Does celiac disease occur in Afro-derived Brazilian populations? Am J Hum Biol 2012;24:710–712.
111. Mora M, Litwin N, Toca M del C, et al. Prevalence of celiac disease: multicentric trial among pediatric population from five urban districts in Argentina. Arch Argent Pediatr 2012;110:490–496.
112. Almeida LM, Castro LC, Uenishi RH, et al. Decreased prevalence of celiac disease among Brazilian elderly. World J Gastroenterol 2013;19:1930–1935.
113. Vázquez H, Paz Temprano M de la, Sugai E, et al. Prevalence of celiac disease and celiac autoimmunity in the Toba Native Amerindian community of Argentina. Can J Gastroenterol Hepatol 2015;29:431–434.
114. Edlinger-Horvat C, Fidler D, Huber W-D, et al. Serological screening for undiagnosed coeliac disease in male adolescents in lower Austria: a population based study. Eur J Pediatr 2005; 164:52–53.
115. Fabiani E, Peruzzi E, Mandolesi A, et al. Anti-human versus anti-guinea pig tissue transglutaminase antibodies as the first-level serological screening test for coeliac disease in the general population. Dig Liver Dis 2004;36:671–676.
116. Tommasini A, Not T, Kiren V, et al. Mass screening for coeliac disease using antihuman transglutaminase antibody assay. Arch Dis Child 2004;89:512–515.
117. Shahbazkhani B, Malekzadeh R, Sotoudeh M, et al. High prevalence of coeliac disease in apparently healthy Iranian blood donors. Eur J Gastroenterol Hepatol 2003; 15:475–478.
118. Ravikumara M, Nootigattu VKT, Sandhu BK. Ninety percent of celiac disease is being missed. J Pediatr Gastroenterol Nutr 2007;45:497–499.
119. Lebwohl B, Murray JA. Gluten introduction, breastfeeding, and celiac disease: back to the drawing board. Am J Gastroenterol 2016;111:12–14.
120. Lionetti E, Catassi C. Co-localization of gluten consumption and HLA-DQ2 and -DQ8 genotypes, a clue to the history of celiac disease. Dig Liver Dis 2014;46:1057–1063.

Reprint requests
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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 Leffler 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

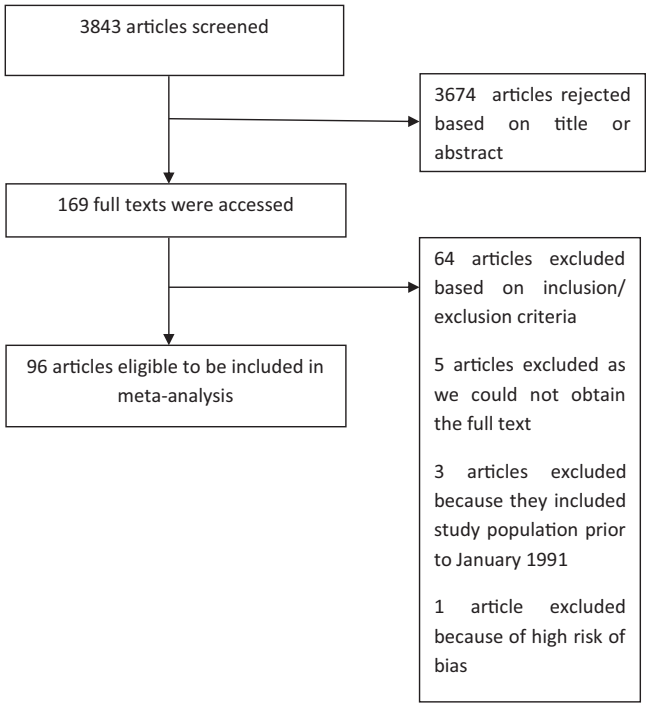
Exploring Heterogeneity

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,[31,37,40,47,48,50,53,54,56,58–60,63,84,93,96,101,110] to 95% in the group with 75% to 99.9% of seropositive individuals undergoing a biopsy,[9,11,34,36,41,55,57,65,66,68,70,71,76,80,82,85,87,90–92,103,105,109,111] and 82% in the group with 50% to 74.9% of seropositive individuals undergoing a biopsy.[10,33,38,39,42,61,74,77,83,88,89,102,115,116]

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[37–39,50,53,55,57,60,63,76,80,85,87,91,93] and 91% for studies with a moderate risk of bias.[9–11,31,33,34,36,40–42,47,48,54,56,58,59,61,65,66,68,70,71,74,77,82–84,88–90,92,96,101–103,105,109–111,115,116] 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%.[9,37,39,53,55,57,59–61,63,70,80,82,88,90,92,93,97,101,102,110,115] 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%.[10,11,31,33,34,36,38,40–42,47,48,50,54,56,58,65,66,68,71,74,76,77,83–85,87,89,91,103,105,109,111,116] 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.