Latitude and Celiac Disease Prevalence: A Meta-analysis and Meta-regression

Short title: Latitude and Celiac Disease

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Abbreviations: AGA, amidated gliadin peptide antibodies; CD, celiac disease; DGP, deamidated gliadin peptide; EMA, endomysial antibodies; HLA, human leukocyte antigen; tTGA, tissue transglutaminase antibodies; NA, not applicable

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Abstract

Background and Aims: Latitudinal gradient effect is described for several autoimmune diseases including celiac disease in the United States. However, the association between latitude and global celiac disease prevalence is unknown. We aimed to explore the association between latitude and serology-based celiac disease prevalence through meta-analysis.

Methods: We searched MEDLINE, Embase, Cochrane, and Scopus databases from their beginning through June 29, 2018, to identify screening studies that targeted a general population sample, used serology-based screening tests, and provided a clear location from which we could assign a latitude. Studies were excluded if sampling was based on symptoms, risk factors, or referral. Study selection and data extraction were performed by independent reviewers. The association measures between latitude and prevalence of serology-based celiac disease were evaluated with random-effects meta-analyses and meta-regression.

Results: Of the identified 4,667 unique citations, 128 studies were included, with 155 prevalence estimates representing 40 countries. Celiac disease was more prevalent at the higher latitudes of 51º to 60º (relative risk, 1.62; 95% CI: 1.09-2.38) and 61º to 70º (relative risk, 2.30; 95% CI: 1.36-3.89) compared with the 41º to 50º reference level. No statistically significant difference was observed in lower latitudes. When latitude was treated as continuous, we found statistically significant association between CD prevalence and latitude overall in the world (RR=1.03, 95% CI: 1.01 – 1.05) and subregional analysis of Europe (RR=1.05, 95% CI: 1.02 – 1.07) and North America (RR=1.1, 95% CI: 1.0 – 1.2).

Conclusions: In this comprehensive review of screening studies, we found that higher latitude was associated with greater serology-based celiac disease prevalence.

Keywords: sprue; serum; tissue transglutaminase; epidemiology

Introduction

Celiac disease (CD) is a prevalent autoimmune disease triggered by ingested gluten. It is seen mostly in people of European, North African, and Middle Eastern descent. CD prevalence is highly heterogeneous[1, 2]. Geoepidemiology of CD can provide insight into pathogenesis and risk factors responsible for its distribution and increasing incidence[3]. Variations in prevalence among populations with similar human leukocyte antigen (HLA) predisposing allele frequencies and genetic backgrounds point to environmental factors that contribute to disease pathogenesis. Previous studies have shown a correlation between gluten consumption and HLA haplotype frequencies that predispose persons to CD[4-6]. A large part of the variation in worldwide prevalence has yet to be explained.

Increasing autoimmunity in higher geographic latitudes has been reported for multiple sclerosis[7], rheumatoid arthritis[8, 9], and inflammatory bowel disease[10]. These associations were linked to less solar exposure and resultant vitamin D deficiency that has been shown to predispose to autoimmune states in several diseases[11, 12]. A study using National Health and Nutrition Examination Survey data reported a South-North gradient of CD seroprevalence in the United States[13]. The gradient was statistically significant after adjustment for race/ethnicity, sex, age, and income[13]. The latitudinal association with worldwide CD prevalence is unknown. Therefore, we conducted a systematic review and a meta-analysis to examine the association of latitude with CD seroprevalence.

Supplemental Material 2. Characteristics of Included Studies

Study	Year of screening	Country	City/Province	Latitude	Age, y	Population	Convenience Sampling Details	Screening Test	Confirmatory Test	No. Screened	No. of Cases	Proportion of Cases
Aberg, 2009[1]	2008	Sweden	Orebro	59.30	20-99	Blood donors		tTGA	EMA	400	5	0.0125
Abu-Zeid, 2014[2]	2008	UAE	Al Ain	24.21	16-70	Convenience sampling	Prenuptial examination	tTGA	EMA	1197	14	0.0117
Abu-Zekry, 2008[3]	2004	Egypt	Cairo	30.05	0-18	Convenience sampling	General outpatient clinic	tTGA	EMA	1500	16	0.0053
Agardh, 2004[4]	2000	Sweden	Malmo	55.61	2-4	General population		tTGA	EMA	652	19	0.0291
Agardh, 2007[5]	2007	Sweden	Malmo	55.61	19-81	General population		tTGA	NA	398	6	0.0151
Agardh, 2009[6]	2000	Sweden	Lund	55.78	50-64	General population	Female patients	tTGA	NA	6481	60	0.0093
Akbari, 2006_1[7]	2004	Iran	Sari	36.33	18-66	General population		tTGA	EMA	1438	3	0.0021
Akbari, 2006_2	2004	Iran	Kerman	30.29	18-66	General population		tTGA	EMA	1361	2	0.0015
Al Hatlani,2015[8]	2014	Saudi Arabia	Eastern Province, National Guard	26.20	6-18	General population		tTGA	NA	1141	32	0.0280
Al-Ajlan, 2016[9]	2013	Saudi Arabia	Riyadh	24.77	20-60	General population		tTGA	EMA	482	9	0.0187
Alarida, 2011[10]	2011	Libya	El Beida	36.7	5-17	General population		tTGA	NA	2920	24	0.0146
Alencar, 2012[11]	2004	Brazil	San Paulo	23.55	18-65	Blood donors		tTGA	EMA	4000	14	0.0082
Alessandrini, 2013_1[12]	2005	Republic of San Marino	Republic of San Marino	43.94	6-14	General population		AGA	EMA	4304	28	0.0033
Alessandrini, 2013_2	2009	Republic of San Marino	Republic of San Marino	43.94	6-10	General population		tTGA	EMA	788	14	0.0065
Al-Hussaini, 2017[13]	2016	Saudi Arabia	Riyadh	24.8	6-15	General population		tTGA	EMA	7932	116	0.0178
Aljebreen, 2013_Al-Qaseem[14]	2008	Saudi Arabia	Al-Qaseem	26.2	16-18	General population		EMA	NA	252	8	0.0317
Aljebreen, 2013_Aseer	2008	Saudi Arabia	Aseer	19.26	16-18	General population		EMA	NA	479	10	0.0209
Aljebreen, 2013_Madinah	2008	Saudi Arabia	Madinah	24.55	16-18	General population		EMA	NA	436	8	0.0183
Almazan, 2015[15]	2012	Spain	Granada	37.18	2-4	General population		tTGA	NA	198	6	0.0303
Almeida, 2013[16]	2011	Brazil	Brasilia	15.77	60-92	General population		tTGA	EMA	946	1	0.0011
Anderson, 2013[17]	2006	Australia	South East Australia	34.66	20-97	General population		tTGA	EMA	2548	27	0.0106
Antunes, 2002[18]	1999	Portugal	Braga	41.55	13-15	General population		tTGA	EMA	536	5	0.0093
Bahari, 2010[19]	2007	Iran	Sistan and Baluchestan Province	29.47	17-65	Blood donors		tTGA	NA	1600	14	0.0088
Bdioui, 2006[20]	2004	Tunisia	Monastir	35.77	17-57	Blood donors		EMA	tTGA	1418	2	0.0014
Bonamiko, 2011[21]	2007	Italy	Rome	41.9	10-14	General population		tTGA	EMA	4048	50	0.0124
Borch, 2000[22]	2000	Sweden	Linkoping	58.41	35-85	General population		EMA	NA	482	9	0.0187
Canavan, 2011[23]	2001	UK	Cambridge	52.21	45-76	General population		EMA	tTGA	7550	88	0.0117
Carlsson, 2001[24]	1997	Sweden	Malmo	55.61	2-4	General population		AGA	EMA	679	13	0.0191
Castano, 2004[25]	2002	Spain	Bizkaia, Cruces	43.29	<3	General population		tTGA	EMA	484	7	0.0145
Catassi, 1994[26]	1993	Italy	Pesaro-Urbino	43.74	11-15	General population		AGA	EMA	3351	20	0.0060
Catassi, 2000[27]	1998	Italy	Alghero	40.56	11-15	General population		AGA	EMA	2096	19	0.0091
Catassi, 2010[28]	1989	USA	Washington County, Maryland	39.63	35-65	General population		tTGA	EMA	3511	16	0.0046
Chin, 2009[29]	1995	Australia	Busselton	33.39	20-79	General population		tTGA	NA	3011	43	0.0143
Choung, 2017[30]	2011	USA	Olmsted County	44.02	18-50	General population		tTGA	EMA	30425	372	0.0111
Cilleruelo, 2002[31]	2000	Spain	Madrid	40.42	10-12	General population		EMA	NA	3378	15	0.0044
Cook, 2000[32]	2000	New Zealand	Christchurch	43.53	>18	General population		EMA	NA	1064	13	0.0122
Corraza, 1997[33]	1997	Republic of San Marino	Republic of San Marino	43.94	18-87	General population		EMA	NA	2237	4	0.0018
Csizmadia, 1999[34]	1997	The Netherlands	Zuid-Holland	51.99	2-4	General population		EMA	NA	6127	75	0.0122
da Conceicao-Machado, 2015[35]	2009	Brazil	Salvador City, Bahia	12.93	11-17	General population		tTGA	NA	1213	7	0.0058
Dalgic, 2011[36]	2008	Turkey	Turkey	39.25	6-17	General population		tTGA	EMA	20190	215	0.0106
Demirceken, 2008[37]	2003	Turkey	Ankara	39.56	2-18	Convenience sampling	General outpatient clinic	tTGA	EMA	1000	10	0.0100
Denghani, 2013[38]	2013	Iran	Shiraz	29.59	6-12	General population		tTGA	NA	1500	30	0.0200
Edlingeer-Horvat, 2005[39]	2002	Austria	Lower Austria	48.3	17-18	Convenience sampling	Compulsory conscript medical examination, all males	tTGA	EMA	7660	26	0.0034
El-Hadi, 2004[40]	2002	UK	Wales	51.83	18-22	General population		tTGA	EMA	1000	6	0.0060
Ertekin, 2005[41]	2005	Turkey	Erzurum	39.9	6-17	General population		tTGA	NA	1263	11	0.0087

extract the latitudinal and longitudinal coordinates, we used Google Maps to select the geographic "centroid" of the study area and the related latitude and longitude of locations. The variable latitude represents the distance of the study from the equator, in the southern or northern hemisphere. Reviewers [M.G.C, C.L.J-K., I.A.H.] evaluated the studies for methodological quality, using a tool that assesses internal and external validity in prevalence studies[18] (Supplemental Material 3).

Statistical Analyses

For studies reporting prevalence by age groups (ie, adults and children), locations, or screening periods, we used each cohort as an independent unit for analysis because they contributed independent information. For studies examining the same population, we included only the most recent or inclusive study or studies with sequential test results, if applicable.

Crude prevalence was determined as the proportion of positive cases to individuals screened. We then normalized the prevalence using log transformation and pooled it using the DerSimonian Laird random-effects methods[19]. Heterogeneity— the variation in study prevalence estimates between studies that is not due to sampling variability—was assessed with the I^2 statistic[20]. Random-effects meta-regression was carried out to calculate the association for seroprevalence and latitude after control for predefined variables, including age group, year of screening, type of test used to diagnose cases, and study region[21]. Age was categorized as *pediatric* (0-18 years) and *adult* (>18 years). Testing method was categorized into 1) sequential with IgA tTGA, AGA, or deamidated gliadin peptide (DGP) antibodies followed by EMA or only EMA testing or 2)

IgA tTGA testing. Latitudes were categorized based on 10º increments from the equator. Latitudes from 0º to 20º were considered 1 category to increase the number of studies included in the category. A latitudinal level of 41º to 50º was set as the reference group to stabilize regression because most studies were conducted within this level. We conducted analyses using latitude and longitude as continuous variables in the regression model for each region and the world. We evaluated the relationship between sample size and prevalence estimates with the funnel plot using the log of the prevalence and Egger's regression test of asymmetry[22]. We used Stata 15 command *metareg* to perform regression on study-level data and *metan* for pooled prevalence estimates. Two tailed P values less than .05 were considered statistically significant. Software Stata version 15.1 (StataCorp LLP, College Station, TX) was used for statistical analysis. A map with study locations colored to represent levels of prevalence was created using QGIS 3.12 (http://qgis.org).

Results

Of the identified 4,667 unique abstracts, we included 155 cohorts from 128 studies that represented 40 countries (Figure 1). The samples used for these cohorts were blood donors (n=26), convenience samples (n=5), and general population (n=124) (Supplemental Material 2). Most studies were from Europe, followed in frequency by Middle East and North Africa (Supplemental Material 4). Most of the studies from Europe and North America provided results based on sequential screening or EMA alone (92/124). Of the 155 cohorts, 65 were pediatric. Prevalence from 1980 through 2016 was available (mean screening year, 2003; range, 1980-2016). Most studies with the screening year before 2000 were from Europe (32/37). Supplemental material 2 provides details of the 128 studies with references included. All studies had low or moderate risk of bias (Supplemental Material 3).

The worldwide prevalence estimate was 0.79% (95% CI: 0.71-0.88) with significant heterogeneity (I^2=91.2%) (Table 1, Figure 2). After controlling for the screening test, age group, screening year, and region, the higher latitudes had a statistically significant association with higher CD seroprevalence (Table 2). The relative risk (RR) of CD was 1.62 (95% CI: 1.09-2.38) in 51º to 60º latitudes and 2.30 (95% CI: 1.36-3.89) in 61º to 70º latitudes compared with the reference level 41º to 50º (Table 2). Relative risk in lower latitude categories did not reach statistical significance (Table 2). Positive latitudinal association was observed in the sub-regional analysis of Europe. When latitude was treated as continuous, we found statistically significant association between CD prevalence and latitude overall in the world (RR=1.03, 95% CI: 1.01 -1.05) and in the sub-regional analysis of Europe (RR=1.05, 95% CI: 1.02 – 1.07) and North America (RR=1.1, 95% CI: 1.0 – 1.2) (Table 3, Supplemental Material 5 and 6). Longitude was not associated with global CD prevalence (RR=1.002, 95% CI: 0.998 - 1.005). All study locations are depicted on a world map in Figure 3 and referenced (Supplemental Material 7).

The visual examination of the funnel plot depicting the log of the prevalence plotted against the estimated standard error showed funnel plot asymmetry with significance (Egger’s regression test, $p < 0.05$) indicating that smaller studies tended to have lower prevalence estimates (Supplemental Material 8).

Discussion

In this study, we found an overall increase in the risk of CD prevalence globally with increasing latitude after controlling for regions and covariates for study level differences. When latitudes were categorized into intervals of 10º latitudinal increments, an association was seen between CD prevalence and latitudes above 40º. In regions with lower latitudinal coordinates, North India and the Arabian Peninsula in the Northern Hemisphere and Brazil in the Southern Hemisphere were found to be high-prevalence regions. The higher latitudes were significantly associated with higher CD seroprevalence in the United States and Europe in regional analyses. The prevalence of CD varies widely across regions, likely because of differences in genetic and environmental factors. Overall, genetic inheritance explains 50% of susceptibility[6] and among the genetic factors, HLA-DQ2 and HLA-DQ8 haplotypes are the major determinants in the pathogenesis of CD[23]. Increased predisposing HLA frequencies tend to aggregate in regions where the duration of historical wheat consumption is longer[4], possibly contributing to higher prevalence rates in these regions. After Europe, studies from the region of the Middle East and North Africa provided most of the prevalence estimates included in the analyses.

Genetic predisposition fails to explain differences among and within some regions in the world. In India, although the CD predisposing HLA-DQ frequencies were similar in Northern, Northeastern and Eastern India, CD is reported to be more prevalent in northern regions where wheat intake is higher[5]. On the other hand, despite wheat consumption per capita being highest in North African and Middle Eastern countries, the

North European regions still have the highest prevalence estimates in this current study. These observations point to combination of factors and unidentified elements that modify disease risk.

Latitude is often used as a surrogate of environmental factors in geoepidemiologic studies. CD shares common mechanisms of antigen presentation and T-cell–mediated immune activation with multiple sclerosis[7] and rheumatoid arthritis[8, 9] whose geographic distributions show latitudinal association[23, 24]. The only study on latitude and CD to our knowledge is from the United States that is located between 20º and 50º north and showed a greater prevalence of CD with higher latitudes[13]. A candidate factor typically associated with the latitudinal coordinate that may have a role in causality is vitamin D–effective solar UV radiation. Skin exposure to solar radiation at UVB wavelengths that is determined by the season and latitude is the major source of 25-hydroxyvitamin D levels in the body in the absence of supplementary intake[25, 26]. Evidence has shown the modulatory effect of vitamin D on the immune system through the inducement and maintenance of tolerogenic immune cells[27, 28]. Multiple sclerosis is one of the well-defined autoimmune diseases with latitudinal association and the protective effect of vitamin D in multiple sclerosis has been extensively investigated[12, 29, 30]. The immunomodulatory effect of vitamin D towards immune tolerance was further supported by the association of incidence and disease activity with vitamin D levels in multiple sclerosis[12, 30], inflammatory bowel diseases[31, 32], rheumatoid arthritis[33] and systemic lupus erythematosus[34]. Vitamin D deficiency in celiac disease, as a fat soluble vitamin in a malabsorptive condition, is common; however, its role in pathogenesis is not known[35-37].

Latitude may be a proxy for socioeconomic status or infection with common viruses. Certain environmental pathogens such as enteroviruses[38, 39] and adenoviruses[40-42] have been shown to be associated with development of CD[43]. Socioeconomic status may result in differences in environmental conditions in complex ways including differential exposure to infections, vaccines, antibiotic use, microbial flora, and gluten consumption, but there are no conclusive data showing an association with socioeconomic status and celiac disease[44-46].

The gradient effect in rheumatoid arthritis and multiple sclerosis is observed to reverse or diminish in countries located at higher latitudes, such as Norway and Sweden[7, 47]. Namatovu et. al. found that childhood CD was more prevalent in the southern latitudes of Sweden than in its northern latitudes and attributed this pattern to differences in awareness and rates of yearly epidemics of viruses[48]. Environmental factors including cultural differences and infections may surpass the effect of latitude associated factors. We did not have finely delineated distributions of prevalence in latitudes above 60° to examine a similar trend in higher latitudes.

This meta-regression analysis did not show a uniform distribution of latitudinal gradient of CD globally. The disease was prevalent between the latitudes of 20º and 30°. Located near this area, Saudi Arabia and Brazil have reported prevalence rates comparable to those of Northern Europe. Increased prevalence and younger age at presentation of rheumatoid arthritis are also observed in countries near the Northern Tropic (23°26′12.4″ north of the equator)[8]. This outcome was attributed to the developmental status of countries and to related environmental exposures such as infections. Despite having high HLA genotype frequencies and one of the highest rankings in per-capita wheat consumption, Iran had a reported prevalence that was not as high as Saudi Arabia, which is located in a lower latitude, or Western European countries (data from http://www.fao.org, accessed April 24, 2019). The reasons for this trend have yet to be explained.

We estimated the worldwide celiac disease serum prevalence at 0.79% with substantial variation (95% CI: 0.71-0.88%, I^2 = 91%). A previous CD study estimated a higher global prevalence[1]. Because a sequential testing strategy was shown to be more sensitive and specific[49-52], we included screening results of sequential testing [53] or the more specific tTG test assay results rather than AGA or less specific tTG test assays[54-56], when available. Additionally, we used criteria that specified inclusion of population samples without risk factors. These differences may account for the lower prevalence estimation in our study compared with previous meta-analysis studies of global or regional prevalence[1, 57]. The other potential reason may be the overrepresentation of small studies as shown in the funnel plot as smaller studies tended to show lower prevalence estimates[58-61]. This phenomenon could also be due to the aggregation of the larger scale studies in more prevalent areas such as Europe and North America.

Strengths

The comprehensive nature of the systematic review of prevalence studies is a major strength of the present study. We included screening year and testing type in our regression analysis to accommodate for known factors associated with prevalence. We included only serum-based screening studies for 2 main reasons. First, CD may be clinically silent, and most cases are undiagnosed. Studies from Northern European regions report increased awareness of CD starting in earlier years[62, 63]. Yet, recent studies have showed that a substantial proportion of CD is undiagnosed in parts of the world where people of North African and Middle Eastern descent predominate[1]. Second, screening studies based on biopsy results tend to have low response rates, and it is difficult to standardize the results. Therefore, our analysis reflects disease prevalence that is independent of region-specific differences in awareness of CD. We included studies with sequential testing that included EMA because this test has been shown to have the highest sensitivity and specificity[16, 17]. Because sequential or EMA alone testing is more specific than IgA tTGA results, we controlled for the type of testing in our models.

Limitations

Our study has some limitations. The latitudes assigned to each location in the present study were not precise. We found considerable heterogeneity between studies. There is a possibility of bias caused by extreme prevalence estimates from small sample studies in higher and lower latitudes. CD is more prevalent in women, but we did not have enough data from all studies to include sex in the analysis. Some regions were not represented in our analysis, including Sub-Saharan Africa and Canada, because either no studies were available or met our inclusion criteria. Although HLA-DQ2 and HLA-DQ8 are known major genetic determinants of CD, data for HLA haplotype distributions were too heterogeneous and were not available for most study locations. Moreover, the provided allele frequencies represented different allele haplotypes. Some of the reported HLA allele frequencies were of certain ethnic populations and minority groups, whereas CD prevalence for corresponding locations provided prevalence for Caucasians. Various studies used different commercial test assays with different cutoffs, and we regarded each test result as positive according to the reporting in respective studies. Some prevalence studies used blood donors and convenience sampling methods which may not always be considered representative of general population; however, we evaluated studies systematically for methodological quality including for assessment of representation of the general population. All included studies had low or moderate risk of study bias.

Conclusions

We found serology-based CD prevalence was greater in higher latitudes away from equator toward south and north, similar to associations observed in chronic autoimmune diseases. Further studies on candidate environmental factors that are latitude-associated including vitamin-D effective UVB exposure, environmental pathogens, and countries' developmental status will advance the understanding of factors responsible for geographical variation of CD prevalence.

Figure Legend

Figure 1. Flow Diagram of Identified Studies

Figure 2. Forest Plot

Figure 3. World map showing the distribution of the studies

Supplemental Material 6. Scatter plot of log-transformed prevalence against latitude and fitted linear prediction. The area of each circle is inversely proportional to the variance of the prevalence of each study location.

Supplemental Material 8. Funnel plot examining publication bias

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Supplemental Material. Results of Univariate and Multivariate Random-Effects Regression [a]

Variable	**Relative Risk (95% CI)**	***P* Value**
Unadjusted		
Latitude	1.01 (1.00 – 1.02)	0.071
Multivariate regression without regions [b]		
Latitude	1.02 (1.00 – 1.03)	0.009
Pediatric age group [d]	1.44 (1.07 – 1.94)	0.018
Testing method, tTG [e]	1.59 (1.10 – 2.32)	0.015
Screening year	1.01 (0.99 – 1.04)	0.356
Multivariate regression with regions [c]		
Latitude	1.03 (1.01 – 1.05)	0.014
Pediatric age group [d]	1.42 (1.03 – 1.96)	0.032
Testing method [e]	1.53 (1.03 – 2.27)	0.034
Screening year	1.02 (0.99 – 1.04)	0.228
Europe (reference)	1	
North Africa and Middle East	1.541 (0.88 – 2.70)	0.228
Latin America and the Caribbean	1.44 (0.61 – 3.42)	0.407
Australia and New Zealand	2.40 (0.84 – 6.88)	0.101
East and South Asia	0.90 (0.33 – 2.47)	0.831
North America	0.96 (0.51 – 1.81)	0.909

[a] Model includes log-transformed prevalence estimates as the dependent variable.

[b] Model includes covariates of latitude, age group, screening year, and testing method.

[c] Model includes covariates of latitude, age group, screening year, test type, and world regions.

[d] Adult age group as reference

[e] Sequential testing as reference

Table 1. Prevalence Estimates for Individual Regions and Latitudinal Intervals

Value	No. of Cohorts (No. of Studies)	Pooled Prevalence Estimate % (95% CI)	I^2,%
World pooled estimate	155 (127)	0.79 (0.71-0.88)	91.2
World region			
North Africa and Middle East	30 (27)	0.96 (0.74-1.23)	89.6
Latin America and the Caribbean	13 (13)	0.51 (0.3-0.88)	89.8
Australia and New Zealand	3 (3)	1.27 (1.02-1.57)	NA
Europe	91 (73)	0.83 (0.72-0.95)	90.4
East and South Asia	7 (5)	0.45 (0.24-0.86)	94.9
North America	11 (6)	0.57 (0.37-0.88)	95.1
Latitudinal interval			
≤20º	9 (9)	0.55 (0.02-1.27)	92.9
>20º to ≤30º	19 (17)	0.98 (0.7-1.36)	90.9
>30º to ≤40º	34 (30)	0.58 (0.44-0.78)	92
>40º to ≤50º	42 (36)	0.67 (0.55-0.81)	90
>50º to ≤60º	37 (31)	0.99 (0.81-1.22)	90.8
>60º to ≤70º	14 (13)	1.24 (0.99-1.54)	83.4

Abbreviation: NA, not available.

Table 2. Adjusted Relative Risk for Latitudinal Intervals

Latitudinal Intervals	No. of Cohorts	Relative Risk (95% CI)
≤20º	9	0.87 (0.29-2.66)
>20º to ≤30º	19	0.95 (0.37-2.40)
>30º to ≤40º	34	0.50 (0.25-1.02)
>40º to ≤50º	42	1.0 (reference)
>50º to ≤60º	37	**1.62 (1.09-2.38)**[a]
>60º to ≤70º	14	**2.30 (1.36-3.89)**[a]

[a] Bold indicates statistical significance.

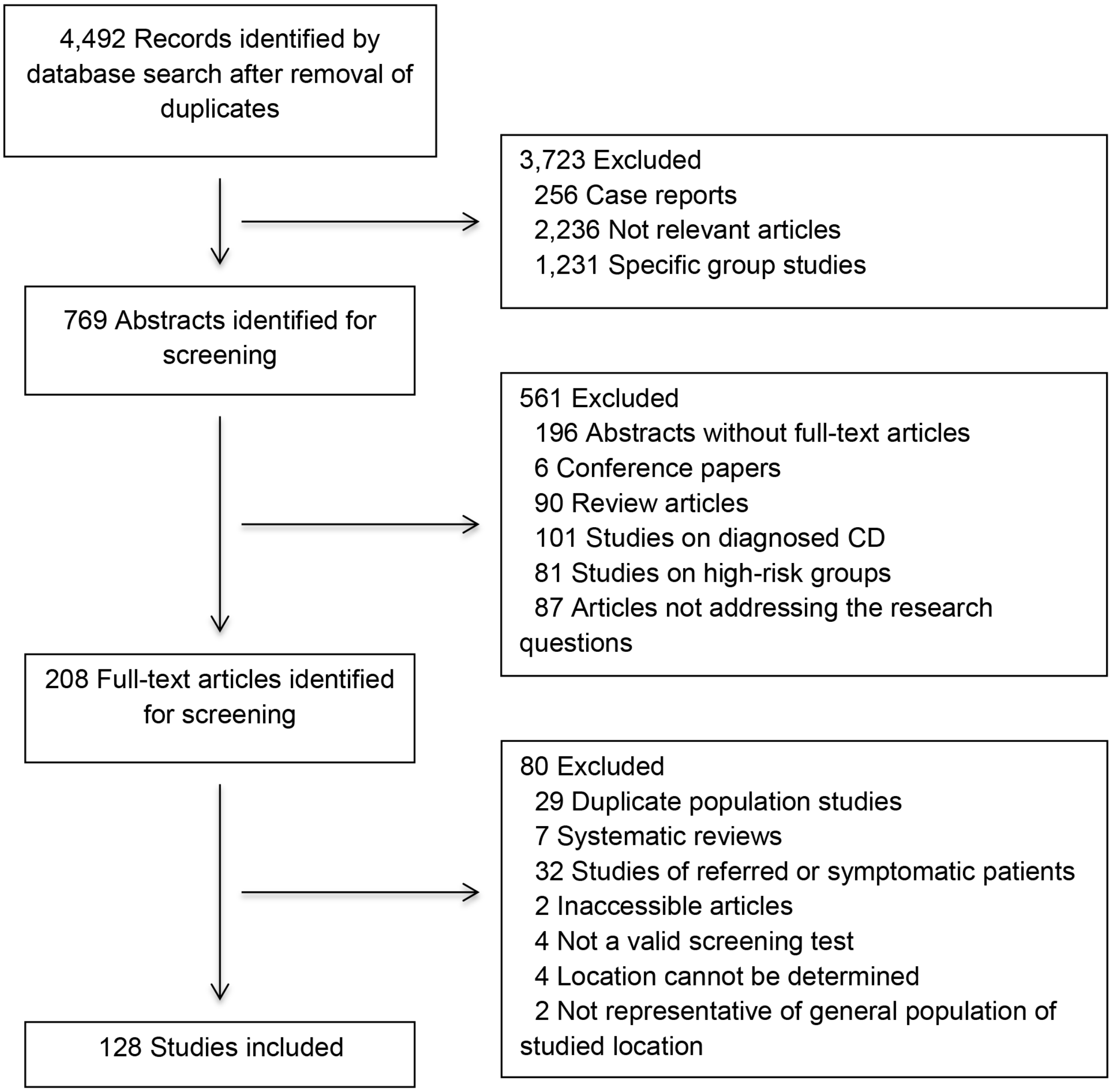
Model includes covariates of age group, screening year, test type, and world regions, with log-transformed prevalence estimates as the dependent variable.

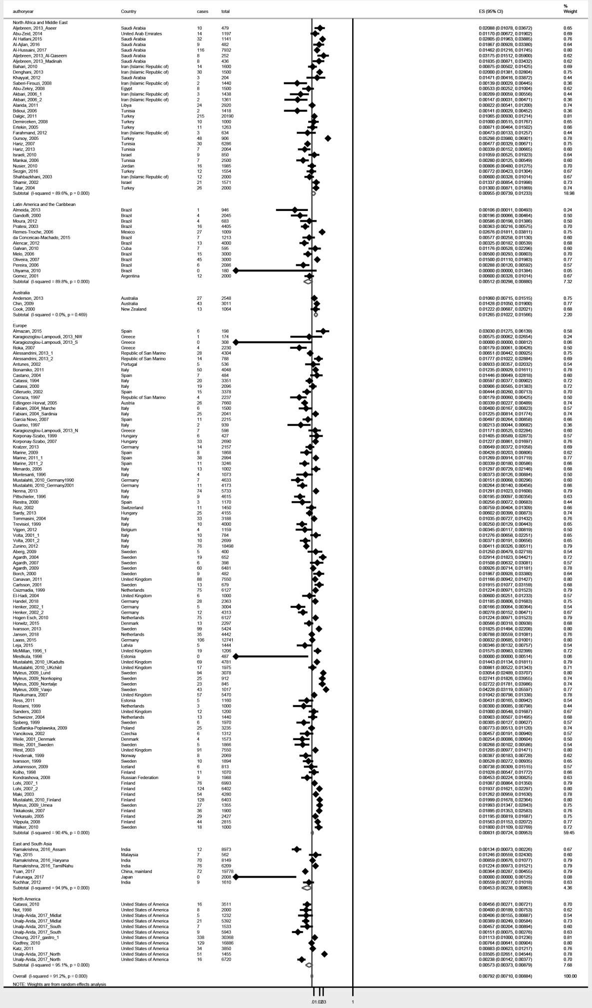
Table 3. Region-Specific and Global Latitudinal Coefficients[a]

Region	Relative Risk (95% CI)	*P* Value
World[a]	1.03 (1.01-1.05)	.014
Europe[b]	1.05 (1.02-1.07)	<.001
North America[b]	1.10 (1.00-1.20)	.05
North Africa and Middle East[b]	1.00 (0.90-1.01)	.11
Latin America and the Caribbean[b]	1.01 (0.93-1.10)	.41
East and South Asia[b]	0.88 (0.59-1.30)	.36

[a] Model includes covariates of age group, screening year, test type, and world regions, with log-transformed prevalence estimates as the dependent variable.
[b] Model includes covariates of age group, screening year, and testing method.

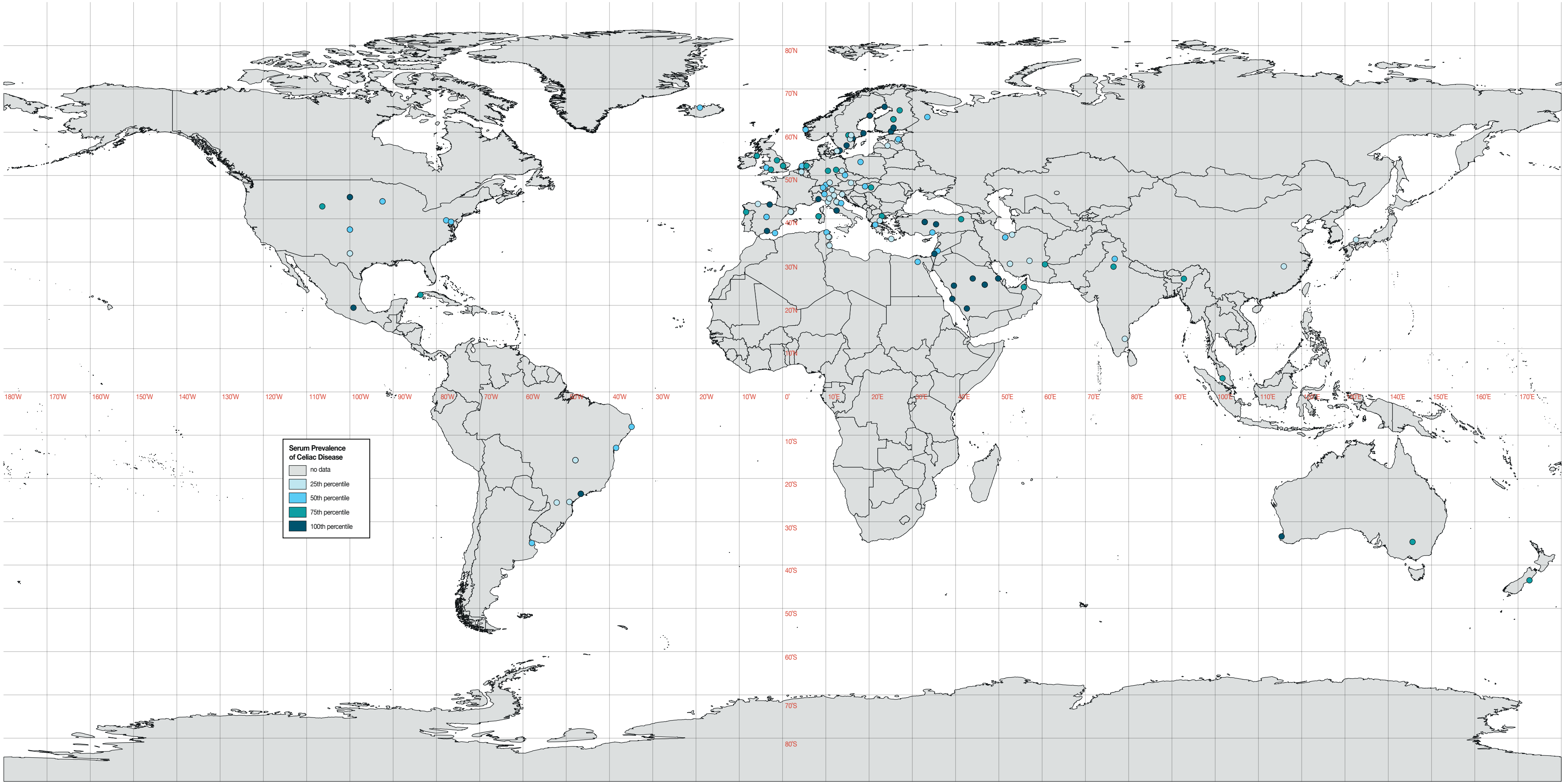
Figure 1. Flow Diagram of Identified Studies





authoryear	Country	cases	total	ES (95% CI)	% Weight
North Africa and Middle East					
Aljebreen, 2013_Aseer	Saudi Arabia	10	479	0.02088 (0.01078, 0.03672)	0.65
Abu-Zeid, 2014	United Arab Emirates	14	1197	0.01170 (0.00672, 0.01902)	0.69
Al Hatlani,2015	Saudi Arabia	32	1141	0.02805 (0.01963, 0.03885)	0.76
Al-Ajlan, 2016	Saudi Arabia	9	482	0.01867 (0.00928, 0.03380)	0.64
Al-Hussaini, 2017	Saudi Arabia	116	7932	0.01462 (0.01216, 0.01745)	0.80
Aljebreen, 2013_Al-Qaseem	Saudi Arabia	8	252	0.03175 (0.01512, 0.05900)	0.62
Aljebreen, 2013_Madinah	Saudi Arabia	8	436	0.01835 (0.00871, 0.03432)	0.62
Bahari, 2010	Iran (Islamic Republic of)	14	1600	0.00875 (0.00502, 0.01425)	0.69
Denghani, 2013	Iran (Islamic Republic of)	30	1500	0.02000 (0.01381, 0.02804)	0.75
Khayyat, 2012	Saudi Arabia	3	204	0.01471 (0.00416, 0.03872)	0.44
Saberi-Firouzi, 2008	Iran (Islamic Republic of)	2	1440	0.00139 (0.00029, 0.00445)	0.36
Abu-Zekry, 2008	Egypt	8	1500	0.00533 (0.00252, 0.01004)	0.62
Akbari, 2006_1	Iran (Islamic Republic of)	3	1438	0.00209 (0.00059, 0.00556)	0.44
Akbari, 2006_2	Iran (Islamic Republic of)	2	1361	0.00147 (0.00031, 0.00471)	0.36
Alarida, 2011	Libya	24	2920	0.00822 (0.00541, 0.01200)	0.74
Bdioui, 2006	Tunisia	2	1418	0.00141 (0.00029, 0.00452)	0.36
Dalgic, 2011	Turkey	215	20190	0.01065 (0.00930, 0.01214)	0.81
Demirceken, 2008	Turkey	10	1000	0.01000 (0.00515, 0.01767)	0.65
Ertekin, 2005	Turkey	11	1263	0.00871 (0.00464, 0.01502)	0.66
Farahmand, 2012	Iran (Islamic Republic of)	3	634	0.00473 (0.00133, 0.01257)	0.44
Gursoy, 2005	Turkey	48	906	0.05298 (0.03980, 0.06901)	0.78
Hariz, 2007	Tunisia	30	6286	0.00477 (0.00329, 0.00671)	0.75
Hariz, 2013	Tunisia	7	2064	0.00339 (0.00152, 0.00665)	0.60
Israeli, 2010	Israel	9	850	0.01059 (0.00525, 0.01923)	0.64
Mankai, 2006	Tunisia	7	2500	0.00280 (0.00125, 0.00549)	0.60
Nusier, 2010	Jordan	16	1985	0.00806 (0.00480, 0.01275)	0.70
Sezgin, 2016	Turkey	12	1554	0.00772 (0.00423, 0.01304)	0.67
Shahbazkhani, 2003	Iran (Islamic Republic of)	12	2000	0.00600 (0.00328, 0.01014)	0.67
Shamir, 2002	Israel	21	1571	0.01337 (0.00854, 0.01998)	0.73
Tatar, 2004	Turkey	26	2000	0.01300 (0.00871, 0.01869)	0.74
Subtotal (I-squared = 89.6%, p = 0.000)				0.00955 (0.00739, 0.01233)	18.98
.					
Latin America and the Caribbean					
Almeida, 2013	Brazil	1	946	0.00106 (0.00011, 0.00493)	0.24
Gandolfi, 2000	Brazil	4	2045	0.00196 (0.00066, 0.00464)	0.50
Moura, 2012	Brazil	4	683	0.00586 (0.00198, 0.01386)	0.50
Pratesi, 2003	Brazil	16	4405	0.00363 (0.00216, 0.00575)	0.70
Remes-Troche, 2006	Mexico	27	1009	0.02676 (0.01811, 0.03811)	0.75
da Conceicao-Machado, 2015	Brazil	7	1213	0.00577 (0.00258, 0.01130)	0.60
Alencar, 2012	Brazil	13	4000	0.00325 (0.00182, 0.00539)	0.68
Galvan, 2010	Cuba	7	595	0.01176 (0.00528, 0.02296)	0.60
Melo, 2006	Brazil	15	3000	0.00500 (0.00293, 0.00803)	0.70
Oliveira, 2007	Brazil	45	3000	0.01500 (0.01110, 0.01983)	0.77
Pereira, 2006	Brazil	6	2086	0.00288 (0.00120, 0.00592)	0.57
Utiyama, 2010	Brazil	0	180	0.00000 (0.00000, 0.01384)	0.05
Gomez, 2001	Argentina	12	2000	0.00600 (0.00328, 0.01014)	0.67
Subtotal (I-squared = 89.8%, p = 0.000)				0.00512 (0.00298, 0.00880)	7.32
.					
Australia					
Anderson, 2013	Australia	27	2548	0.01060 (0.00715, 0.01515)	0.75
Chin, 2009	Australia	43	3011	0.01428 (0.01050, 0.01900)	0.77
Cook, 2000	New Zealand	13	1064	0.01222 (0.00687, 0.02021)	0.68
Subtotal (I-squared = 0.0%, p = 0.469)				0.01265 (0.01022, 0.01566)	2.20
.					
Europe					
Almazan, 2015	Spain	6	198	0.03030 (0.01275, 0.06139)	0.58
Karagiozoglou-Lampoudi, 2013_NW	Greece	1	174	0.00575 (0.00062, 0.02654)	0.24
Karagiozoglou-Lampoudi, 2013_S	Greece	0	308	0.00000 (0.00000, 0.00812)	0.06
Roka, 2007	Greece	4	2230	0.00179 (0.00061, 0.00426)	0.50
Alessandrini, 2013_1	Republic of San Marino	28	4304	0.00651 (0.00442, 0.00925)	0.75
Alessandrini, 2013_2	Republic of San Marino	14	788	0.01777 (0.01022, 0.02884)	0.69
Antunes, 2002	Portugal	5	536	0.00933 (0.00357, 0.02032)	0.54
Bonamiko, 2011	Italy	50	4048	0.01235 (0.00929, 0.01611)	0.78
Castano, 2004	Spain	7	484	0.01446 (0.00649, 0.02818)	0.60
Catassi, 1994	Italy	20	3351	0.00597 (0.00377, 0.00902)	0.72
Catassi, 2000	Italy	19	2096	0.00906 (0.00565, 0.01383)	0.72
Cilleruelo, 2002	Spain	15	3378	0.00444 (0.00260, 0.00713)	0.70
Corraza, 1997	Republic of San Marino	4	2237	0.00179 (0.00060, 0.00425)	0.50
Edlingeer-Horvat, 2005	Austria	26	7660	0.00339 (0.00227, 0.00489)	0.74
Fabiani, 2004_Marche	Italy	6	1500	0.00400 (0.00167, 0.00823)	0.57
Fabiani, 2004_Sardinia	Italy	25	2041	0.01225 (0.00814, 0.01774)	0.74
Garcia Novo, 2007	Spain	11	2215	0.00497 (0.00264, 0.00858)	0.66
Guariso, 1997	Italy	2	939	0.00213 (0.00044, 0.00682)	0.36
Karagiozoglou-Lampoudi, 2013_N	Greece	7	598	0.01171 (0.00525, 0.02284)	0.60
Korponay-Szabo, 1999	Hungary	6	427	0.01405 (0.00589, 0.02873)	0.57
Korponay-Szabo, 2007	Hungary	33	2690	0.01227 (0.00861, 0.01697)	0.76
Kratzer, 2013	Germany	14	2157	0.00649 (0.00372, 0.01058)	0.69
Marine, 2009	Spain	8	1868	0.00428 (0.00203, 0.00806)	0.62
Marine, 2011_1	Spain	38	2994	0.01269 (0.00914, 0.01719)	0.77
Marine, 2011_2	Spain	11	3246	0.00339 (0.00180, 0.00586)	0.66
Menardo, 2006	Italy	13	1002	0.01297 (0.00729, 0.02146)	0.68
Montesanti, 1996	Italy	4	1073	0.00373 (0.00126, 0.00884)	0.50
Mustalahti, 2010_Germany1990	Germany	7	4633	0.00151 (0.00068, 0.00296)	0.60
Mustalahti, 2010_Germany2001	Germany	11	4173	0.00264 (0.00140, 0.00456)	0.66
Nenna, 2013	Italy	74	5733	0.01291 (0.01023, 0.01608)	0.79
Pittschieler, 1996	Italy	9	4615	0.00195 (0.00097, 0.00356)	0.63
Riestra, 2000	Spain	3	1170	0.00256 (0.00072, 0.00683)	0.44
Rutz, 2002	Switzerland	11	1450	0.00759 (0.00404, 0.01309)	0.66
Sardy, 2013	Hungary	25	4155	0.00602 (0.00399, 0.00873)	0.74
Tommasini, 2004	Italy	33	3188	0.01035 (0.00727, 0.01432)	0.76
Trevisiol, 1999	Italy	10	4000	0.00250 (0.00129, 0.00443)	0.65
Vijgen, 2012	Belgium	4	1159	0.00345 (0.00117, 0.00819)	0.50
Volta, 2001_1	Italy	10	784	0.01276 (0.00658, 0.02251)	0.65
Volta, 2001_2	Italy	10	2699	0.00371 (0.00191, 0.00656)	0.65
Zunino, 2012	Italy	76	18498	0.00411 (0.00326, 0.00511)	0.79
Aberg, 2009	Sweden	5	400	0.01250 (0.00479, 0.02718)	0.54
Agardh, 2004	Sweden	19	652	0.02914 (0.01823, 0.04421)	0.72
Agardh, 2007	Sweden	6	398	0.01508 (0.00632, 0.03081)	0.57
Agardh, 2009	Sweden	60	6481	0.00926 (0.00714, 0.01181)	0.78
Borch, 2000	Sweden	9	482	0.01867 (0.00928, 0.03380)	0.64
Canavan, 2011	United Kingdom	88	7550	0.01166 (0.00942, 0.01427)	0.80
Carlsson, 2001	Sweden	13	679	0.01915 (0.01077, 0.03159)	0.68
Csizmadia, 1999	Netherlands	75	6127	0.01224 (0.00971, 0.01523)	0.79
El-Hadi, 2004	United Kingdom	6	1000	0.00600 (0.00251, 0.01233)	0.57
Handel, 2018	Germany	28	2363	0.01185 (0.00806, 0.01683)	0.75
Henker, 2002_1	Germany	5	3004	0.00166 (0.00064, 0.00364)	0.54
Henker, 2002_2	Germany	12	4313	0.00278 (0.00152, 0.00471)	0.67
Hogen Esch, 2010	Netherlands	75	6127	0.01224 (0.00971, 0.01523)	0.79
Horwitz, 2015	Denmark	13	2297	0.00566 (0.00318, 0.00938)	0.68
Ivarsson, 2013	Sweden	99	5424	0.01825 (0.01494, 0.02208)	0.80
Jansen, 2018	Netherlands	35	4442	0.00788 (0.00559, 0.01081)	0.76
Laass, 2015	Germany	106	12741	0.00832 (0.00685, 0.01001)	0.80
Leja, 2015	Latvia	5	1444	0.00346 (0.00132, 0.00757)	0.54
McMillan, 1996_1	United Kingdom	19	1206	0.01575 (0.00983, 0.02399)	0.72
Mestkula, 1998	Estonia	0	487	0.00000 (0.00000, 0.00514)	0.06
Mustalahti, 2010_UKadults	United Kingdom	69	4781	0.01443 (0.01134, 0.01811)	0.79
Mustalahti, 2010_UKchild	United Kingdom	17	1975	0.00861 (0.00522, 0.01343)	0.71
Myleus, 2009_Lund	Sweden	94	3078	0.03054 (0.02489, 0.03707)	0.80
Myleus, 2009_Norrkoping	Sweden	25	912	0.02741 (0.01826, 0.03955)	0.74
Myleus, 2009_Norrtalje	Sweden	23	845	0.02722 (0.01781, 0.03986)	0.74
Myleus, 2009_Vaxjo	Sweden	43	1017	0.04228 (0.03119, 0.05597)	0.77
Ravikumara, 2007	United Kingdom	57	5470	0.01042 (0.00798, 0.01338)	0.78
Ress, 2011	Estonia	5	1160	0.00431 (0.00165, 0.00942)	0.54
Rostami, 1999	Netherlands	3	1000	0.00300 (0.00085, 0.00798)	0.44
Sanders, 2003	United Kingdom	12	1200	0.01000 (0.00548, 0.01687)	0.67
Schweizer, 2004	Netherlands	13	1440	0.00903 (0.00507, 0.01495)	0.68
Sjoberg, 1999	Sweden	6	1970	0.00305 (0.00127, 0.00627)	0.57
Szaflarska-Poplawska, 2009	Poland	25	3235	0.00773 (0.00513, 0.01120)	0.74
Vancikova, 2002	Czechia	6	1312	0.00457 (0.00191, 0.00940)	0.57
Weile, 2001_Denmark	Denmark	4	1573	0.00254 (0.00086, 0.00604)	0.50
Weile, 2001_Sweden	Sweden	5	1866	0.00268 (0.00102, 0.00586)	0.54
West, 2003	United Kingdom	91	7550	0.01205 (0.00977, 0.01471)	0.80
Hovdenak, 1999	Norway	8	2069	0.00387 (0.00183, 0.00728)	0.62
Ivarsson, 1999	Sweden	10	1894	0.00528 (0.00272, 0.00935)	0.65
Johannsson, 2009	Iceland	6	813	0.00738 (0.00309, 0.01515)	0.57
Kolho, 1998	Finland	11	1070	0.01028 (0.00547, 0.01772)	0.66
Kondrashova, 2008	Russian Federation	9	1988	0.00453 (0.00224, 0.00825)	0.63
Lohi, 2007_1	Finland	76	6993	0.01087 (0.00864, 0.01350)	0.79
Lohi, 2007_2	Finland	124	6402	0.01937 (0.01621, 0.02297)	0.80
Maki, 2003	Finland	54	4280	0.01262 (0.00959, 0.01630)	0.78
Mustalahti, 2010_Finland	Finland	128	6403	0.01999 (0.01678, 0.02364)	0.80
Myleus, 2009_Umea	Sweden	27	1355	0.01993 (0.01347, 0.02843)	0.75
Tikkakoski, 2007	Finland	36	1900	0.01895 (0.01353, 0.02583)	0.76
Verkasalo, 2005	Finland	29	2427	0.01195 (0.00819, 0.01687)	0.75
Vilppula, 2008	Finland	44	2815	0.01563 (0.01153, 0.02072)	0.77
Walker, 2010	Sweden	18	1000	0.01800 (0.01109, 0.02769)	0.72
Subtotal (I-squared = 90.4%, p = 0.000)				0.00831 (0.00724, 0.00953)	59.45
.					
East and South Asia					
Ramakrishna, 2016_Assam	India	12	8973	0.00134 (0.00073, 0.00226)	0.67
Yap, 2015	Malaysia	7	562	0.01246 (0.00559, 0.02430)	0.60
Ramakrishna, 2016_Haryana	India	70	8149	0.00859 (0.00676, 0.01077)	0.79
Ramakrishna, 2016_TamilNahu	India	76	6209	0.01224 (0.00973, 0.01521)	0.79
Yuan, 2017	China, mainland	72	19778	0.00364 (0.00287, 0.00455)	0.79
Fukunaga, 2017	Japan	0	2008	0.00000 (0.00000, 0.00125)	0.08
Kochhar, 2012	India	9	1610	0.00559 (0.00277, 0.01018)	0.63
Subtotal (I-squared = 94.9%, p = 0.000)				0.00453 (0.00238, 0.00863)	4.36
.					
North America					
Catassi, 2010	United States of America	16	3511	0.00456 (0.00271, 0.00721)	0.70
Not, 1998	United States of America	8	2000	0.00400 (0.00189, 0.00753)	0.62
Unalp-Arida, 2017_Midlat	United States of America	5	1232	0.00406 (0.00155, 0.00887)	0.54
Unalp-Arida, 2017_Midlat	United States of America	21	5392	0.00389 (0.00249, 0.00584)	0.73
Unalp-Arida, 2017_South	United States of America	7	1533	0.00457 (0.00204, 0.00894)	0.60
Unalp-Arida, 2017_South	United States of America	9	5943	0.00151 (0.00075, 0.00276)	0.63
Choung, 2017_gastro_1	United States of America	338	30368	0.01113 (0.01000, 0.01236)	0.81
Godfrey, 2010	United States of America	129	16886	0.00764 (0.00641, 0.00904)	0.80
Katz, 2011	United States of America	34	3850	0.00883 (0.00623, 0.01217)	0.76
Unalp-Arida, 2017_North	United States of America	51	1455	0.03505 (0.02651, 0.04544)	0.78
Unalp-Arida, 2017_North	United States of America	16	6720	0.00238 (0.00142, 0.00377)	0.70
Subtotal (I-squared = 95.1%, p = 0.000)				0.00573 (0.00373, 0.00879)	7.68
.					
Overall (I-squared = 91.2%, p = 0.000)				0.00792 (0.00710, 0.00884)	100.00

NOTE: Weights are from random effects analysis


Serum Prevalence of Celiac Disease
no data
25th percentile
50th percentile
75th percentile
100th percentile
80°N
70°N
60°N
50°N
40°N
30°N
20°N
10°N
0°
10°S
20°S
30°S
40°S
50°S
60°S
70°S
80°S
180°W
170°W
160°W
150°W
140°W
130°W
120°W
110°W
100°W
90°W
80°W
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100°E
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120°E
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140°E
150°E
160°E
170°E

Supplemental Material 2. Characteristics of Included Studies

Study	Year of screening	Country	City/Province	Latitude	Age, y	Population	Convenience Sampling Details	Screening Test	Confirmatory Test	No. Screened	No. of Cases	Proportion of Cases
Aberg, 2009[1]	2008	Sweden	Orebro	59.30	20-99	Blood donors		tTGA	EMA	400	5	0.0125
Abu-Zeid, 2014[2]	2008	UAE	Al Ain	24.21	16-70	Convenience sampling	Prenuptial examination	tTGA	EMA	1197	14	0.0117
Abu-Zekry, 2008[3]	2004	Egypt	Cairo	30.05	0-18	Convenience sampling	General outpatient clinic	tTGA	EMA	1500	16	0.0053
Agardh, 2004[4]	2000	Sweden	Malmo	55.61	2-4	General population		tTGA	EMA	652	19	0.0291
Agardh, 2007[5]	2007	Sweden	Malmo	55.61	19-81	General population		tTGA	NA	398	6	0.0151
Agardh, 2009[6]	2000	Sweden	Lund	55.78	50-64	General population	Female patients	tTGA	NA	6481	60	0.0093
Akbari, 2006_1[7]	2004	Iran	Sari	36.33	18-66	General population		tTGA	EMA	1438	3	0.0021
Akbari, 2006_2	2004	Iran	Kerman	30.29	18-66	General population		tTGA	EMA	1361	2	0.0015
Al Hatlani,2015[8]	2014	Saudi Arabia	Eastern Province, National Guard	26.20	6-18	General population		tTGA	NA	1141	32	0.0280
Al-Ajlan, 2016[9]	2013	Saudi Arabia	Riyadh	24.77	20-60	General population		tTGA	EMA	482	9	0.0187
Alarida, 2011[10]	2011	Libya	El Beida	36.7	5-17	General population		tTGA	NA	2920	24	0.0146
Alencar, 2012[11]	2004	Brazil	San Paulo	23.55	18-65	Blood donors		tTGA	EMA	4000	14	0.0082
Alessandrini, 2013_1[12]	2005	Republic of San Marino	Republic of San Marino	43.94	6-14	General population		AGA	EMA	4304	28	0.0033
Alessandrini, 2013_2	2009	Republic of San Marino	Republic of San Marino	43.94	6-10	General population		tTGA	EMA	788	14	0.0065
Al-Hussaini, 2017[13]	2016	Saudi Arabia	Riyadh	24.8	6-15	General population		tTGA	EMA	7932	116	0.0178
Aljebreen, 2013_Al-Qaseem[14]	2008	Saudi Arabia	Al-Qaseem	26.2	16-18	General population		EMA	NA	252	8	0.0317
Aljebreen, 2013_Aseer	2008	Saudi Arabia	Aseer	19.26	16-18	General population		EMA	NA	479	10	0.0209
Aljebreen, 2013_Madinah	2008	Saudi Arabia	Madinah	24.55	16-18	General population		EMA	NA	436	8	0.0183
Almazan, 2015[15]	2012	Spain	Granada	37.18	2-4	General population		tTGA	NA	198	6	0.0303
Almeida, 2013[16]	2011	Brazil	Brasilia	15.77	60-92	General population		tTGA	EMA	946	1	0.0011
Anderson, 2013[17]	2006	Australia	South East Australia	34.66	20-97	General population		tTGA	EMA	2548	27	0.0106
Antunes, 2002[18]	1999	Portugal	Braga	41.55	13-15	General population		tTGA	EMA	536	5	0.0093
Bahari, 2010[19]	2007	Iran	Sistan and Baluchestan Province	29.47	17-65	Blood donors		tTGA	NA	1600	14	0.0088
Bdioui, 2006[20]	2004	Tunisia	Monastir	35.77	17-57	Blood donors		EMA	tTGA	1418	2	0.0014
Bonamiko, 2011[21]	2007	Italy	Rome	41.9	10-14	General population		tTGA	EMA	4048	50	0.0124
Borch, 2000[22]	2000	Sweden	Linkoping	58.41	35-85	General population		EMA	NA	482	9	0.0187
Canavan, 2011[23]	2001	UK	Cambridge	52.21	45-76	General population		EMA	tTGA	7550	88	0.0117
Carlsson, 2001[24]	1997	Sweden	Malmo	55.61	2-4	General population		AGA	EMA	679	13	0.0191
Castano, 2004[25]	2002	Spain	Bizkaia, Cruces	43.29	<3	General population		tTGA	EMA	484	7	0.0145
Catassi, 1994[26]	1993	Italy	Pesaro-Urbino	43.74	11-15	General population		AGA	EMA	3351	20	0.0060
Catassi, 2000[27]	1998	Italy	Alghero	40.56	11-15	General population		AGA	EMA	2096	19	0.0091
Catassi, 2010[28]	1989	USA	Washington County, Maryland	39.63	35-65	General population		tTGA	EMA	3511	16	0.0046
Chin, 2009[29]	1995	Australia	Busselton	33.39	20-79	General population		tTGA	NA	3011	43	0.0143
Choung, 2017[30]	2011	USA	Olmsted County	44.02	18-50	General population		tTGA	EMA	30425	372	0.0111
Cilleruelo, 2002[31]	2000	Spain	Madrid	40.42	10-12	General population		EMA	NA	3378	15	0.0044
Cook, 2000[32]	2000	New Zealand	Christchurch	43.53	>18	General population		EMA	NA	1064	13	0.0122
Corraza, 1997[33]	1997	Republic of San Marino	Republic of San Marino	43.94	18-87	General population		EMA	NA	2237	4	0.0018
Csizmadia, 1999[34]	1997	The Netherlands	Zuid-Holland	51.99	2-4	General population		EMA	NA	6127	75	0.0122
da Conceicao-Machado, 2015[35]	2009	Brazil	Salvador City, Bahia	12.93	11-17	General population		tTGA	NA	1213	7	0.0058
Dalgic, 2011[36]	2008	Turkey	Turkey	39.25	6-17	General population		tTGA	EMA	20190	215	0.0106
Demirceken, 2008[37]	2003	Turkey	Ankara	39.56	2-18	Convenience sampling	General outpatient clinic	tTGA	EMA	1000	10	0.0100
Denghani, 2013[38]	2013	Iran	Shiraz	29.59	6-12	General population		tTGA	NA	1500	30	0.0200
Edlingeer-Horvat, 2005[39]	2002	Austria	Lower Austria	48.3	17-18	Convenience sampling	Compulsory conscript medical examination, all males	tTGA	EMA	7660	26	0.0034
El-Hadi, 2004[40]	2002	UK	Wales	51.83	18-22	General population		tTGA	EMA	1000	6	0.0060
Ertekin, 2005[41]	2005	Turkey	Erzurum	39.9	6-17	General population		tTGA	NA	1263	11	0.0087

Fabiani, 2004_Marche[42]	2001	Italy	Camerano, Marche	43.61	1-91	General population		tTGA	EMA	1500	6	0.0040
Fabiani, 2004_Sardinia	2001	Italy	Alghero, Sardinia	40.56	10-19	General population		tTGA	EMA	2041	25	0.0122
Farahmand, 2012[43]	2008	Iran	Tehran	35.7	7-18	General population		tTGA	NA	634	3	0.0047
Fukunaga, 2017[44]	2016	Japan	Shimane	35.16	25-80	General population		tTGA	EMA	2008	0	0.0000
Galvan, 2010[45]	2007	Cuba	Pinar del Rio	22.42	3	General population		tTGA	NA	595	7	0.0118
Gandolfi, 2000[46]	1998	Brazil	Brasilia	15.77	18-61	Blood donors		AGA	EMA	2045	4	0.0020
Garcia Novo, 2007[47]	2002	Spain	Madrid	40.42	18-65	General population		tTGA	NA	2215	11	0.0050
Godfrey, 2010[48]	2001	USA	Olmsted County	44.02	50-88	General population		tTGA	EMA	16886	129	0.0076
Gomez, 2001[49]	2000	Argentina	La Plata, Buenos Aires	34.92	16-79	General population		AGA	EMA	2000	12	0.0060
Guariso, 1997[50]	1995	Italy	Padua	45.4	10-15	General population		AGA	EMA	939	2	0.0021
Gursoy, 2005[51]	2004	Turkey	Kayseri	38.73	20-59	Convenience sampling	Routine examination for general medical reasons	tTGA	NA	906	48	0.0530
Handel, 2018[52]	2015	Germany	Leipzig	51.3	1-18	General population		tTGA	EMA	2363	28	0.0118
Hariz, 2007[53]	2004	Tunisia	Ariana	36.86	7-13	General population		tTGA	EMA	6286	30	0.0048
Hariz, 2013[54]	2011	Tunisia	Djerba	33.81	6-12	General population		tTGA	EMA	2064	7	0.0034
Henker, 2002_1[55]	1995	Germany	Dresden	51.07	5-12	General population		EMA	NA	3004	5	0.0017
Henker, 2002_2	1995	Germany	Dresden	51.07	17-64	Blood donors		EMA	NA	4313	12	0.0028
Hogen Esch, 2010[56]	1998	The Netherlands	The Netherlands	52.24	2-4	General population		EMA	NA	6127	75	0.0122
Horwitz, 2015[57]	2012	Denmark	Southwestern Copenhagen	55.66	24-76	General population		tTGA	NA	2297	13	0.0057
Hovdenak, 1999[58]	1999	Norway	Bergen	60.58	18-67	Blood donors		AGA	EMA	2069	8	0.0039
Israeli, 2010[59]	2003	Israel	Israel	31.91	18	Convenience sampling	Military recruits	tTGA	NA	850	9	0.0106
Ivarsson, 1999[60]	1994	Sweden	Umea-North Sweden	63.83	25-74	General population		AGA	EMA	1894	10	0.0053
Ivarsson, 2013[61]	2010	Sweden	Sweden	59.34	12	General population		tTGA	EMA	5424	99	0.0183
Jansen, 2018[62]	2013	The Netherlands	Rotterdam	52.2	6	General population		tTGA	EMA	4442	35	0.0079
Johannsson, 2009[63]	2007	Iceland	Akureyri	65.68	17-64	Blood donors		tTGA	NA	813	6	0.0074
Karagiozoglou-Lampoudi, 2013_N[64]	2013	Greece	Thessaloniki	40.62	2-6	General population		tTGA	EMA	598	7	0.0117
Karagiozoglou-Lampoudi, 2013_NW	2013	Greece	Agrinio	38.62	2-6	General population		tTGA	EMA	174	1	0.0057
Karagiozoglou-Lampoudi, 2013_S	2013	Greece	Herakleion	35.34	2-6	General population		tTGA	EMA	308	0	0.0000
Katz, 2011[65]	2011	USA	Natrona County	42.86	>18	General population		tTGA	EMA	3850	34	0.0088
Khayyat, 2012[66]	2010	Saudi Arabia	Jeddah	21.49	14-78	Blood donors		tTGA	NA	204	3	0.0147
Kochhar, 2012[67]	2011	India	Chandigarh	30.73	20-41	Blood donors		tTGA	NA	1610	9	0.0056
Kolho, 1998[68]	1996	Finland	Helsinki	60.18	NA	General population		EMA	NA	1070	11	0.0103
Kondrashova, 2008[69]	2001	Russia	Russian Karelia Region	63.50	6-18	General population		tTGA	EMA	1988	9	0.0045
Korponay-Szabo, 1999[70]	1999	Hungary	Budapest	47.49	3-6	General population		EMA	NA	427	6	0.0141
Korponay-Szabo, 2007[71]	2005	Hungary	Jasz-Nagykun-Szolnok County	47.23	6	General population		tTGA	EMA	2690	33	0.0123
Kratzer, 2013[72]	2002	Germany	Leutkirch	47.82	18-65	General population		tTGA	NA	2157	17	0.0065
Laass, 2015[73]	2006	Germany	Germany	51.08	1-17	General population		tTGA	NA	12741	106	0.0083
Leja, 2015[74]	2012	Latvia	Latvia	56.90	24-74	General population		tTGA	EMA	1444	5	0.0035
Lohi, 2007_1[75]	1980	Finland	Finland	62.98	30-95	General population		tTGA	EMA	6993	76	0.0109
Lohi, 2007_2	2001	Finland	Finland	62.98	30-95	General population		tTGA	EMA	6402	124	0.0194
Maki, 2003[76]	1994	Finland	Northern Finland, Oulu	65.05	7-16	General population		tTGA	EMA	4280	54	0.0126
Mankai, 2006[77]	2003	Tunisia	Sousse	35.83	16-63	Blood donors		AGA	EMA	2500	7	0.0028
Marine, 2009[78]	2005	Spain	Terrassa	41.56	30-40	Convenience sampling	Workers in health department	tTGA+EMA	EMA	1868	8	0.0043
Marine, 2011_1[79]	2007	Spain	Catalonia	41.63	1-19	General population		tTGA	NA	2994	38	0.0127
Marine, 2011_2	2007	Spain	Catalonia	41.63	19-99	General population		tTGA	NA	3246	11	0.0034
McMillan, 1996_1[80]	1983	UK	Belfast	54.53	15-64	General population		EMA	NA	1206	19	0.0158
Melo, 2006[81]	2002	Brazil	San Paulo	23.55	18-45	Blood donors		tTGA	EMA	3000	15	0.0050
Menardo, 2006[82]	2003	Italy	Carcare	44.55	13-90	General population		tTGA	EMA	1002	13	0.0130
Mestkula, 1998[83]	1996	Estonia	Southern Estonia	57.94	9-15	General population		AGA	EMA	487	0	0.0000
Montesanti, 1996[84]	1994	Italy	Lucca	43.88	10-15	General population		AGA	EMA	1073	4	0.0037
Moura, 2012[85]	2009	Brazil	Recife	8.06	18-30	Convenience sampling		tTGA	EMA	683	5	0.0059
Mustalahti, 2010_Finland[86]	2001	Finland	Finland	62.98	30-93	General population		tTGA	EMA	6403	128	0.0200
Mustalahti, 2010_Germany1990	1990	Germany	Ausburg	48.34	25-74	General population		tTGA	EMA	4633	7	0.0015
Mustalahti, 2010_Germany2001	2001	Germany	Ausburg	48.34	25-74	General population		tTGA	EMA	4173	11	0.0026
Mustalahti, 2010_UKadults	1987	UK	Northern Ireland	54.53	25-64	General population		tTGA	EMA	4781	69	0.0144
Mustalahti, 2010_UKchild	2000	UK	Northern Ireland	54.53	12-15	General population		tTGA	EMA	1975	17	0.0086

Myleus, 2009_Lund[87]	2006	Sweden	Lund	55.78	12	General population		tTGA	EMA	3078	94	0.0305
Myleus, 2009_Norrkoping	2006	Sweden	Norrkoping	58.59	12	General population		tTGA	EMA	912	25	0.0274
Myleus, 2009_Norrtalje	2006	Sweden	Norrtalje	59.76	12	General population		tTGA	EMA	845	23	0.0272
Myleus, 2009_Umea	2006	Sweden	Umea	63.83	12	General population		tTGA	EMA	1355	27	0.0199
Myleus, 2009_Vaxjo	2006	Sweden	Vaxjo	56.94	12	General population		tTGA	EMA	1017	43	0.0423
Nenna, 2013[88]	2010	Italy	Rome	41.9	2-8	General population		tTGA	EMA	5733	74	0.0129
Not, 1998[89]	1996	USA	Baltimore, Maryland	39.3	19-48	Blood donors		tTGA	EMA	2000	8	0.0040
Nusier, 2010[90]	2006	Jordan	Irbid City	32.56	6-10	General population		tTGA	EMA	1985	16	0.0081
Oliveira, 2007[91]	2004	Brazil	San Paulo	23.55	18-65	Blood donors		tTGA	NA	3000	45	0.0150
Pereira, 2006[92]	2001	Brazil	Curitiba	25.42	20-62	Blood donors		tTGA	EMA	2086	6	0.0029
Pittschieler, 1996[93]	1996	Italy	South Tyrol	46.7	18-82	General population		AGA	EMA	4615	9	0.0020
Pratesi, 2003[94]	2000	Brazil	Brasilia	15.77	1-60	General population		EMA	NA	4405	16	0.0036
Ramakrishna, 2016_TamilNahu[95]	2012	India	Tamil Nadu	12.26	18-100	General population		tTGA	NA	8973	12	0.0013
Ramakrishna, 2016_Haryana	2013	India	Haryana	28.93	18-100	General population		tTGA	NA	6209	76	0.0086
Ramakrishna, 2016_Assam	2013	India	Assam	26.14	18-100	General population		tTGA	NA	8149	70	0.0122
Ravikumara, 2007[96]	2000	UK	Avon, Southwest UK	51.35	8	General population		tTGA	EMA	5470	57	0.0104
Remes-Troche, 2006[97]	2004	Mexico	Mexico City	19.45	17-64	Blood donors		tTGA	NA	1009	27	0.0268
Ress, 2011[98]	1999	Estonia	Tartu County	58.37	9-15	General population		tTGA	NA	1160	5	0.0043
Riestra, 2000[99]	1998	Spain	Langreo, Austrias	43.42	2-89	General population		AGA/NA	EMA	1170	3	0.0026
Roka, 2007[100]	2006	Greece	Thessaly	39.56	18-80	General population		tTGA	EMA	2230	4	0.0018
Rostami, 1999[101]	1998	The Netherlands	Arnhem, Nijmegen	51.92	18-100	Blood donors		EMA	NA	1000	3	0.0030
Rutz, 2002[102]	2000	Switzerland	Canton of St Gallen	47.19	11-18	General population		tTGA	EMA	1450	11	0.0076
Saberi-Firouzi, 2008[103]	2004	Iran	Shiraz	29.61	20-83	General population		tTGA	EMA	1440	2	0.0014
Sanders, 2003[104]	2001	UK	South Yorkshire	53.51	16-91	General population		tTGA	EMA	1200	12	0.0100
Sardy, 2013[105]	2002	Hungary	Budapest	47.49	-	Blood donors		tTGA	EMA	4155	25	0.0060
Schweizer, 2004[106]	1997	The Netherlands	Amsterdam, Doerinchem, Maastricht	52.24	20-59	General population		tTGA	EMA	1440	14	0.0090
Sezgin, 2016[107]	2013	Turkey	Mersin	36.83	18-82	General population		tTGA	NA	1554	12	0.0077
Shahbazkhani, 2003[108]	1999	Iran	Tehran	35.7	18-65	Blood donors		AGA	EMA	2000	12	0.0060
Shamir, 2002[109]	2001	Israel	Israel	31.91	18-76	Blood donors		tTGA	EMA	1571	21	0.0134
Sjoberg, 1999[110]	1997	Sweden	Linkoping	58.41	18-70	Blood donors		AGA	EMA	1970	6	0.0030
Szaflarska-Poplawska, 2009[111]	2009	Poland	Bydgoszcz	53.12	7-10	General population		EMA	NA	3235	25	0.0077
Tatar, 2004[112]	2001	Turkey	Ankara	39.96	18-65	Blood donors		tTGA	NA	2000	26	0.0130
Tikkakoski, 2007[113]	2004	Finland	Helsinki	60.18	18-64	General population		tTGA	EMA	1900	36	0.0189
Tommasini, 2004[114]	2000	Italy	Trieste	45.65	6-12	General population		tTGA	EMA	3188	33	0.0104
Trevisiol, 1999[115]	1998	Italy	Trieste	45.65	18-60	Blood donors		EMA	NA	4000	10	0.0025
Unalp-Arida, 2017_Midlat[116]	2014	USA	Mid Latitude	37.5	20-100	General population		tTGA	EMA	5392	21	0.0041
Unalp-Arida, 2017_Midlat	2014	USA	Mid Latitude	37.5	6-19	General population		tTGA	EMA	1232	5	0.0039
Unalp-Arida, 2017_North	2014	USA	North	45	20-100	General population		tTGA	EMA	6720	51	0.0024
Unalp-Arida, 2017_North	2014	USA	North	45	6-19	General population		tTGA	EMA	1455	16	0.0351
Unalp-Arida, 2017_South	2014	USA	South	32	20-100	General population		tTGA	EMA	5943	7	0.0015
Unalp-Arida, 2017_South	2014	USA	South	32	6-19	General population		tTGA	EMA	1533	9	0.0046
Utiyama, 2010[117]	2010	Brazil	Mangueirinha Reserve	25.56	2-86	General population		EMA	NA	180	0	0.0000
Vancikova, 2002[118]	2001	Czech Republic	Prague	50.07	18-60	Blood donors		tTGA	EMA	1312	6	0.0046
Verkasalo, 2005[119]	2001	Finland	Finland	62.98	24-39	General population		tTGA	EMA	2427	29	0.0119
Vijgen, 2012[120]	2006	Belgium	Belgium	46.7	1-19	General population		tTGA	EMA	1159	4	0.0035
Vilppula, 2009[121]	2002	Finland	Paijat-Hame	61.05	52-74	General population		tTGA	EMA	2815	44	0.0156
Volta, 2001_1[122]	1992	Italy	Campogalliano	44.69	12-25	General population		EMA	NA	784	10	0.0128
Volta, 2001_2	1992	Italy	Campogalliano	44.69	25-65	General population		EMA	NA	2699	10	0.0037
Walker, 2010[123]	1998	Sweden	Kalix and Haparanda	65.87	20-80	General population		tTGA	EMA	1000	18	0.0180
Weile, 2001_Denmark[124]	2001	Denmark	Denmark	55.62	18-65	Blood donors		AGA	EMA	1573	4	0.0025
Weile, 2001_Sweden	2001	Sweden	Sweden	59.34	18-65	Blood donors		AGA	EMA	1866	5	0.0027
West, 2003[125]	1995	UK	Cambridge	52.21	45-76	General population		EMA	TGA	7550	91	0.0121
Yap, 2015[126]	2014	Malaysia	Kuala Lumpur	3.15	18-30	General population		tTGA	EMA	562	7	0.0125
Yuan, 2017[127]	2013	China	Nanchang	29	18-20	General population		DGP	TGA	19778	72	0.0036
Zunino, 2012[128]	2011	Italy	Bergamo	45.7	19-62	Blood donors		tTGA	EMA	18498	76	0.0041

Abbreviations: AGA, amidated gliadin peptide antibody; DGP, deamidated gliadin peptide; EMA, endomysial antibodies; NA, not available; tTGA, tissue transglutaminase antibodies; UAE, United Arab Emirates; UK, United Kingdom; USA, United States of America..

Supplemental Material 6. List of References

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