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Patient and Community Health Global Burden in a World With More Celiac Disease




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Celiac disease is one of the most common life-long disorders worldwide, with a prevalence mostly ranging between 0.7% and 2.9% in the general population and a higher frequency in females and well-defined at-risk groups, such as relatives of affected individuals and patients with autoimmune comorbidities. Increasing clinical detection is facilitated by improving awareness, implementation of a case-finding approach, and serology availability for screening at-risk patients, among other factors. Nevertheless, due to huge clinical variability, many celiac disease cases still escape diagnosis in most countries, unless actively searched by proactive policies. The burden of celiac disease is increasing, as is the need for better longitudinal care. Pediatric screening of the general population could represent the road ahead for an efficient intervention of secondary prevention aimed to reduce the social and health burden of celiac disease. This review analyses the epidemiology of celiac disease continent by continent, discusses current strategies to improve the detection of celiac disease, and highlights challenges related to the burden of celiac disease globally.

Keywords: Celiac Disease; Epidemiology; Prevalence; Incidence; Screening; Case-Finding; Disease Burden.

Until a few decades ago, celiac disease (CeD) was regarded as a rare disease typical of European countries, with an estimated prevalence of 1:4000–1:8000. The subsequent evolution of research, particularly the development of sensitive and simple diagnostic tools, such as tissue transglutaminase (TTG) IgA antibodies, unmasked a completely different story: CeD is one of the most common life-long disorders, with a prevalence mostly ranging between 0.7% and 2.9% in the general population and a higher frequency in females and in well-defined at-risk groups, such as relatives of affected individuals and patients with autoimmune comorbidities; the disease has a worldwide distribution, even though the local prevalence varies according to genetic and environmental factors; still today, due to huge clinical variability, many CeD cases escape diagnosis unless actively searched for by means of proactive policies.[1]

This review analyzes the current distribution of CeD continent by continent, discusses current strategies to improve the detection of CeD, and highlights challenges related to the burden of CeD globally.

Definitions

For the sake of clarity, the terms used repeatedly throughout this review are defined as follows:

Celiac autoimmunity: Positivity of serologic CeD markers, particularly of TTG IgA antibodies and anti-endomysial antibodies (anti-EMAs) (small intestinal biopsy not necessarily performed).

Prevalence of CeD: The total number of individuals in a population who have CeD at a specific time period, either diagnosed or subclinical, usually expressed as a percentage of the population.

Incidence of CeD: The number of individuals who are newly diagnosed with CeD during a particular time period (usually 1 year).

CeD detection rate: The proportion of CeD cases that are diagnosed on a clinical basis compared with the overall prevalence of the disease in a given population.

Abbreviations used in this paper: **CeD, celiac disease; EMA, endomysial antibody; TTG, tissue transglutaminase; GFD, gluten-free diet.**

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Screening: Identification of unrecognized CeD by means of the application of noninvasive tests, usually serum TTG IgA antibodies and total IgA antibodies, which can be performed easily. Individuals with positive or suspicious findings must be referred for diagnosis and treatment.

CeD case finding: The process of looking for disease identification among people showing symptoms or conditions compatible with CeD. It is, in principle but not necessarily, a "patient-initiated" pathway to diagnosis.

Methods

In this narrative review, focused on the epidemiology and the burden of CeD on a worldwide basis, we independently identified the most relevant published articles, including cross-sectional, prospective, and retrospective studies; cohort studies; and systematic reviews and meta-analysis investigating the incidence; prevalence; and detection rates of CeD around the world. The review was restricted to articles written in English. The research was conducted on PubMed, Embase, and Scopus databases using the following Medical Subject Headings terms: *celiac disease* and *epidemiology*, *screening*, *incidence*, *prevalence*, and *burden*.

Celiac Disease Epidemiology in America

CeD incidence and prevalence at the population level has been reported in the United States. Limited data (usually based on serology-only diagnosis and/or using convenience sampling) are available from Canada and Mexico and some countries in Central America and South America. Epidemiology from most of the Caribbean countries remains unknown. Available evidence supports that CeD is common, can develop at any age, risk varies within countries, there are racial and ethnic differences, and clinical diagnosis is lower than seroprevalence in most countries (significant burden of undiagnosed CeD). Therefore, the burden of CeD in America is variable and the challenges by region or country are at different stages of complexity (eg, need for longitudinal care due to higher detection of cases in the United States vs need for better awareness and availability of serology tests in Central America to increase detection).

North America

The prevalence of CeD in the United States has been estimated to be 0.7%.[2] There is evidence that clinical diagnosis of CeD is increasing in the midwest and perhaps there is less hidden CeD in the entire United States.[3,4] Investigation of potential reasons for regional differences in a large and diverse country like the United States is complex. According to the National Health and Nutrition Examination Survey (2009–2014), with 22,277 participants 6 years and older, CeD was more common among individuals who lived at latitudes of 35°–39° North (odds ratio, 3.2) or at latitudes of 40° North or more (odd ratio, 5.4) than individuals who lived at latitudes below 35° North.[5] Similar results were found in meta-analysis of serology-based CeD studies representing 40 countries, with higher risk of CeD at latitudes 51°–70° compared with the 41°–50° reference latitudes.[6] However, CeD relative prevalence was found to be positively correlated with median income, urban area, and proximity to CeD specialty care, but negatively correlated with Black race, Latino ethnicity, and median Social Deprivation Index.[7] Therefore, sociodemographic variables should be considered when planning programs to increase detection and health care of CeD in the community. Furthermore, the TEDDY (The Environmental Determinants of Diabetes in the Young) study confirmed high regional variability in cumulative incidence of CeD in children, the incidence by age 10 years in Colorado was 2.4% among children with DQ2.5 and/or DQ8.1 enrolled prospectively from birth. Children in Colorado had a 2.5-fold higher risk of CeD compared with Washington State, adjusted for HLA genotype, sex, and family history.[8] This finding is not unique to the United States, as similar regional differences were seen among children enrolled in Sweden, Finland, and Germany. Furthermore, although CeD awareness has improved over the years in the United States, significant knowledge gaps and care disparities persist in certain populations, for example, ethnic and racial minority groups and older adults.[9]

CeD appears to be common in Canada. CeD was confirmed in 2.4% of 9695 patients referred for evaluation of gastrointestinal symptoms requiring elective upper endoscopy with duodenal biopsies.[10] A large population-based study in Alberta (2012–2020) reported an incidence of CeD autoimmunity (defined by positive TTG IgA antibodies) of 33.8 per 100,000 person-years (12.9 for persons with TTG IgA antibodies $\geq$10 times the upper limit of normal). Mean annual percentage change was 6.2% from 2015 to 2020.[11] This is consistent with rising incidence throughout the Western world.[12] Population-based studies from Canada are necessary but difficult to execute, in part due to limitations related to the structure and variables included in some population-based health administrative databases, with risk of misclassification using diagnostic codes compared with biopsy-proven diagnosis.[13]

CeD epidemiology in Mexico remains to be fully elucidated. A serology-based study among 1009 consecutive healthy blood donors in a tertiary referral facility in Mexico City demonstrated a 2.7% frequency of TTG IgA antibody–positive individuals and 0.59% double-positive (both TTG IgA antibodies and EMA).[14,15]

Central America and Caribbean

A transition from a dietary culture based on maize with beans and rice to a wheat-containing diet might be happening in Central American countries.[16] Theoretically, this could lead to a rise in the frequency of CeD in this area. So far, information about the frequency of CeD is limited to case reports of CeD in some of these countries, suggesting either low prevalence or high burden of undiagnosed CeD. At the present time, CeD is not a priority for public health in these nations. Thus, population-based studies are nonexistent in countries like Belize, Guatemala, El Salvador,

Honduras, Costa Rica, Nicaragua, Panama, or the Caribbean countries.

South America

Prevalence of CeD among 2000 individuals attending prenuptial examination in the La Plata region, Buenos Aires province, Argentina, between 1998 and 2000 was 0.55% after biopsy confirmation, with the prevalence in women double that in men.[17] A subsequent study in the same region using TTG IgA antibodies as first-line serology followed by EMA testing and biopsy confirmation among 1000 individuals confirmed the prevalence of 0.5%.[18] The prevalence of biopsy-confirmed CeD was 1.2% among 2219 children aged 3–16 years, for whom presurgical tests or physical certificates for sports had been requested in the province of Buenos Aires.[19] Among 144 individuals from the Toba native Amerindian community in Argentina, biopsy-proven CeD was reported in 2% and the estimated mean gluten consumption was 43 g/d.[20]

The prevalence of CeD based on biopsy confirmation among blood donors in São Paolo, Brazil, was 0.35% and 0.46% in 2 studies including 4000 and 3000 individuals, respectively.[21,22] No positive tests for EMAs were observed among 860 individuals from sub-Saharan African-derived Brazilian communities in Northeastern Brazil.[23] In contrast, biopsy-proven diagnosis was 1.3% among Southern Brazilian Mennonites.[24] This finding highlights the need to consider regional, ethnic, and racial CeD prevalence variations within a country and the risk of generalization of estimates to the entire country population in the absence of well-designed population-based studies. The seroprevalence for TTG IgA antibodies and EMAs was 1.32% among 228 blood donors in Bogota, Colombia.[25] However, a different study among 981 healthy individuals in Colombia reported that none were positive for TTG IgA antibodies or EMAs.[26] Thus, the population prevalence of CeD in Colombia remains unknown. A seroprevalence study in individuals aged 18–29 years living in 26 cities in Peru reported a prevalence of 1.2% based on positive TTG IgA antibodies.[27] In Chile, several case series described clinical characteristic of patients with CeD and 1 serology-based study, the National Health Survey 2009–2010 reported a prevalence of 0.76% of positive TTG IgA antibodies in individuals older than 15 years.[28–30] Epidemiology data are limited to case series in Venezuela.[31] No studies are available in Bolivia, Paraguay, Ecuador, and Uruguay.

Celiac Disease Epidemiology in Europe

As reported in a recent meta-analysis, the overall incidence of CeD has been increasing in Europe over time and is now higher than 12.7 per 100,000 person-years in most European countries.[12] During the period 2010–2014, twenty times more patients were diagnosed than during 1975–1979 in the United Kingdom. The largest increase in diagnosis rates occurred in young women, older adults, and Asian immigrants.[32] In Sweden, the mean age-standardized incidence rate during the period 1990–2015 was 19.0 per 100,000 person-years (95% CI, 17.3–20.8). The incidence reached a peak in 1994 for both sexes and a second higher peak in 2002–2003 for females and in 2006 for males. The lifetime risk of developing CeD was 1.8% (2.3% in females and 1.4% in males).[33] In children, large increases in the incidence of diagnosed CeD across Europe have reached 50 per 100,000 person-years in Scandinavia and Spain, with stabilization in some (notably Sweden and Finland).[34] The increasing incidence of CeD in Europe should not be interpreted as evidence of higher frequency of the disease exclusively. Rather this finding may also depend on the improvement of the diagnostics, particularly availability of sensitive and simple serologic test, such as TTG IgA antibody determination, and increased awareness of the high clinical variability of the disease among physicians and the general audience.

After the development of sensitive serologic diagnostic tools, first the anti-gliadin antibodies and then EMAs and TTG IgA antibodies, CeD epidemiology has been more properly investigated by means of serologic screening of general population samples. During the 1990s, Europe, particularly Italy and Sweden, was the homeland of the first screening studies aimed to determine the overall prevalence of CeD.[35,36] In the year 2010, a European multicenter CeD screening on adults reported an overall estimated prevalence of 1.0% (95% CI, 0.9%–1.1%), with wide intercountry variations: CeD prevalence was 2.4% in Finland (95% CI, 2.0%–2.8%), 0.3% in Germany (95% CI, 0.1%–0.4%), and 0.7% in Italy (95% CI, 0.4%–1.0%).[37] Epidemiologic surveys performed during these past years found a more homogenous situation, as summarized below, with a trend toward increasing prevalence of CeD in several countries.

During the years 2015–2020, a large, nationwide, multicenter CeD screening was performed in Italy on 9008 school-aged children (ie, aged 5–11 years) screened at schools in 8 different towns. The first-level screening test was the determination of HLA-related predisposing genotypes HLA-DQ2 and -DQ8, followed by serum IgA class anti–TTG IgA plus total IgA in genetically predisposed children, and eventually EMA determination and small intestinal biopsy in selected cases (according to the European Society for Paediatric Gastroenterology Hepatology and Nutrition diagnostic protocol).[38] In this study, the overall prevalence of CeD was 1.62% (95% CI, 1.39%–1.86%), 1.62% (95% CI, 1.25%–2.06%) in the north of Italy, 1.36% (95% CI, 1.04%–1.75%) in the center, and 1.93% (95% CI, 1.50%–2.45%) in the south, with a statistical difference between central and south Italy ($P = .0482$).[39] The percentage of CeD cases diagnosed before the school screening, that is, the so-called "visible part of the CeD iceberg," was only 35%.[40] In 2 different birth cohorts of 12-year-old Swedish students, the overall prevalence of CeD was 2.2% and 2.9%, respectively.[41] Among 3-year-old Swedish children, the percentage of clinically detected CeD compared with the overall prevalence of disease was fairly low (29%).[42] In Tromsø, Norway, 12,981 adults participated in a population-based CeD serologic screening. The prevalence of previously diagnosed CeD was 0.37%. In addition, the prevalence of previously undiagnosed CeD was 1.10%. Thus, 1.47% of this

Norwegian population sample had CeD, of whom 75% were previously undiagnosed.[43] In the German Health Interview and Examination Survey, 12,741 children and adolescents were studied for CeD-specific autoantibodies and total IgA. Of them, 9 (0.07%) had a reported history of CeD. An elevated concentration of TTG IgA antibodies was found in 91 children with a normal IgA concentration and in 7 with IgA deficiency. The prevalence of undiagnosed CeD, based on positive autoantibody findings, was 0.8% (95% CI, 0.6%–1.0%), and the overall prevalence of the disease was 0.9%.[44] In The Netherlands, 4442 children (median age, 6.0 years) participating in a population-based prospective cohort study were screened for serum TTG IgA. Those with a positive result underwent full clinical evaluation. Forty-nine were eventually diagnosed with CeD, with a prevalence of undetected CeD in this population sample of 0.91% (cases of known CeD were not counted in this study).[45] In Spain, a recent study found a CeD prevalence of 1.62% in children aged 10–12 years. This was an underestimate because only HLA-DQ2–positive (and not HLA-DQ8–positive) children were tested for CeD. Interestingly, approximately 75% of CeD children were already diagnosed at age 2–3 years, and the remaining seroconverted between 2 and 3 years and 10 and 12 years.[46] In summary, at the population level, the prevalence of CeD in Europe ranges between 0.9% and 2.8%, with a median value of approximately 1.6%. Of all these cases, on average, only approximately 30% are clinically diagnosed in the pediatric age group.

As mentioned previously, studies suggest that the overall prevalence of CeD has been increasing during the last decades in some Western countries (Figure 1),[40,47–51] as clearly exemplified by the data collected in Italy. In a pioneer multicenter, country-wide study performed from 1992 through 1994, 17,201 Italian students aged 6–15 years underwent CeD screening by means of combined determination of serum IgG and IgA anti-gliadin antibody test. CeD was diagnosed in 82 subjects. The prevalence of undiagnosed CeD was 0.48%, 1 in 210 subjects, and overall prevalence of CeD, including previously diagnosed CeD cases, was 0.54%, that is, 1 in 184 subjects. At that time, the ratio of known to undiagnosed CeD cases was 1 to 7. As reported many years later in a validation study, the IgA anti-gliadin antibody test, compared with a TTG IgA antibodies screening, underestimated CeD prevalence by 39%. After adjustment for this underestimation, the 1992–1994 CeD prevalence was 0.88%.[40] Compared with the recent estimates (CeD prevalence, 1.62%),[39] the prevalence of CeD has almost doubled in Italy in <30 years, for reasons that are currently unclear.

Celiac Disease Epidemiology in Africa

Epidemiologic data on CeD in Africa are available from a few countries, most of them located in the northern part of the continent. A systematic review pooling data from 7 African populations (15,775 subjects) reported lower CeD figures compared with Western countries, with a CeD seroprevalence of 1.1% (95% CI, 0.4%–2.2%) and a biopsy-confirmed prevalence of 0.5% (95% CI, 0.2%–0.9%) (7902 subjects,4 studies).[52]

Nevertheless, the highest prevalence of CeD worldwide has been described in the Saharawis, a small community of Arab-Berber origin living in Western Sahara. In 1998, a serologic screening based on EMA testing, with intestinal biopsy confirmation in EMA-positive subjects, found CeD in 5.6% of Saharawi children (n = 989; mean ± SD age, 7.4 ± 3.8 years).[53] Furthermore, a follow-up study confirmed the presence of CeD in 8.5% of first-degree relatives of affected Saharawi children.[54] The causes of such a huge frequency of CeD in the Saharawis are unknown. It has been hypothesized that the abrupt and recent change in the dietary pattern of this population (from a low- to high-gluten diet) might have played a role.[53] At the opposite extreme, there are data from Burkina Faso, 600 subjects (aged 15–53 years) among the Mossi population (1 of the 3 ethnic groups of Burkina Faso) were serologically screened (with both TTG IgA antibodies and EMAs), but none tested positive.[55] Because wheat-based products represent the staple food for both the Saharawi and the Mossi populations, the reasons for these differences of CeD prevalence may be related to genetic background. Indeed, HLA CeD-predisposing genes were observed in a high proportion of the Saharawis[56] (a population with a high degree of consanguinity), while the same alleles show a very low frequency among the Mossi.[55]

Frequency of CeD has also been well defined in Libya, where a large screening of 2920 students (1341 aged 5–8 years and 1579 aged 9–17 years) found a prevalence of 0.79% (95% CI, 0.47–1.11).[57] Studies from Tunisia report variable prevalence data, ranging from 0.14% in adults (n = 1328 healthy blood donors)[58] up to 0.63% in children from the district of Ariana (n = 6286; mean ± SD age, 9.7 ± 3 years).[59] A subsequent screening study in Tunisia, based on a rapid immunochromatographic TTG IgA antibodies test, detected a seroprevalence of 0.34% and a biopsy-based prevalence of 0.29% in 2064 school children (aged 6–12 years) living in the island of Djerba.[60] Only sporadic reports or studies based on a case-finding strategy (limited to symptomatic or at-risk populations) are available from other African, particularly sub-Saharan, countries. Data from Sudan suggest a high seroprevalence of CeD in selected groups of symptomatic subjects. Among 172 patients with gastrointestinal or extraintestinal symptoms investigated at the Red Sea Medical Center Laboratory (Port Sudan), 128 (74%) showed positivity of anti-gliadin antibody and/or TTG IgA antibodies test.[61] CeD serology was positive in 6.97% of Sudanese children with type 1 diabetes, with a histologic confirmation in 76.5% of them.[62]

Celiac Disease Epidemiology in Asia

Asia is the largest of the world's continents, covering approximately 30% of the Earth's land area and roughly 60% of the total population.[63] It is paradoxical that CeD is thought to be uncommon in Asia, despite Asia being the home of the world's first farmers, where the first grain was cultivated in the Fertile Crescent. Asia is divided geographically into 5 regions, namely South Asia, East Asia, Southeast Asia, Central Asia, and Western Asia. Due to the heterogeneity of the population, their genetic makeup,

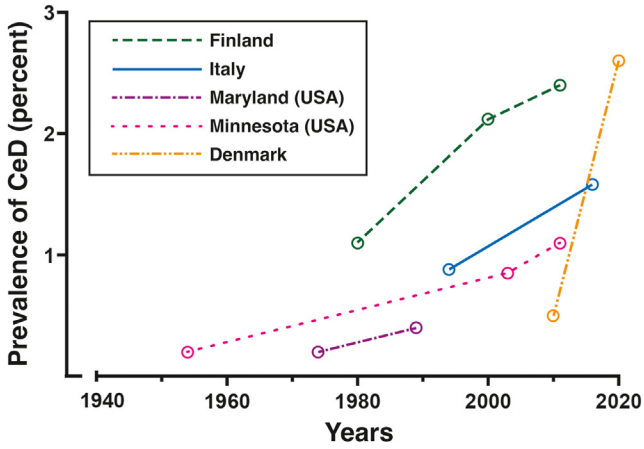

Figure 1. Trends in the prevalence of CeD in different countries.[40,43,47,48,50,51]

economic conditions, and dietary habits, the epidemiology of CeD is different in different parts of Asia. Wider acceptance and availability of serologic tests have led not only to more recognition of CeD in many Asian countries, but also to population-based studies in several Asian countries, such as Turkey, Iran, Israel, Jordan, and India.[64]

South Asia

Among all the Asian countries, CeD is well known in India, more often in the northern part of India, where wheat is the staple diet. Two population-based studies from the northern part of India, one in children by Sood et al[65] and another in adults by Makharia et al,[66] found the prevalence of CeD to be 1 in 310 and 1 in 96, respectively. Later, a pan-India study including 23,331 healthy adults from 3 different regions of India found a regional variation in the prevalence of CeD, more common in the northern part of India (1.23%) compared with only 0.10% in the southern part of India. Interestingly, the distribution of HLA-DQ2 and HLA-DQ8 was similar in these 2 regions and the difference in the prevalence was attributed to the consumption of wheat being higher in the northern part than in the southern part of India.[67] To explore this further, if exposure to the wheat is the main reason for lower prevalence of CeD in the southern part of India, a study is underway among second-generation South Indians who have migrated to the northern part of India.

Southeast Asia

In a study from Vietnam, Zanella et al[68] reported that 1% of 1961 Vietnamese children were TTG IgA antibody–positive, but none were positive for EMAs. One study from Malaysia revealed the seroprevalence of CeD to be 1.2% among 562 young, healthy volunteers who were tested for CeD.[69]

East Asia

Despite China being the highest producer of wheat and 1 in 5 Chinese people (22%) having the HLA-DQ2 gene, at least in the northern part of China, CeD was thought to be exceedingly uncommon in China until recently.[70] There has been a recent surge in interest among Chinese investigators exploring the prevalence of CeD in China. A study including 19,778 adolescents and young adults (aged 16–25 years) from 27 geographic regions in China reported 2.19% of participants had at least 1 positive celiac serologic test, including 1.8% for IgG anti-deamidated gliadin peptide antibody and 0.36% for TTG IgA antibodies. Interestingly, the positivity rate of celiac antibody was 12 times higher among the participants of northern provinces, such as Shandong, Shaanxi, and Henan, where wheat has been the staple diet.[71] Zhou et al[72] reported seroprevalence and prevalence of biopsy-confirmed CeD to be 1.27% (95% CI, 0.81%–1.73%) and 0.35% (95% Cl, 0.11%–0.59%), respectively, among 2277 inpatients with gastrointestinal symptoms. Furthermore, 2.8% of 246 patients with diarrhea-predominant irritable bowel syndrome were reported to have CeD.[73]

A systematic review of 18 studies from China reported the seroprevalence of CeD in the general population and high-risk populations (eg, patients with autoimmune conditions, chronic gastrointestinal symptoms, anemia, low body mass index, or short stature) to be 0.27% (95% CI, 0.02%–0.71%) and 8.3% (95% CI, 4.9%–12.5%), respectively—higher in northern China than southern China.[74] One of the paradoxical observations in Asia was the much lower prevalence of CeD in Japan than the other parts of Asia from where studies are available.[75] In 2018, Fukunaga et al[76] described only 2 biopsy-confirmed CeD cases in a study of 2055 subjects, including 2008 asymptomatic individuals and 47 adults with chronic abdominal symptoms.

Western Asia and Middle East Countries

Until 20 years ago, CeD was reported as a rare condition in the so-called "Fertile Crescent" area (including Middle Eastern countries), which is considered the place of origin of agriculture practices and wheat domestication. Recent studies have described a prevalence similar to European countries in some of these countries (particularly Iran). A high prevalence of CeD in the general population (1.5%–3%) has been found in different screening studies performed in Saudi Arabia.[77] In addition, a systematic review and meta-analysis of 63 studies including 36,833 participants reported the seroprevalence and prevalence of biopsy-confirmed CeD in Iran to be 3% and 2%, respectively.[78] A prevalence of biopsy-proven CeD of 1.5% was found among 999 Lebanese adults who underwent upper endoscopy for several reasons (including symptoms, positive serology, or other risk factors).[79] The prevalence of CeD in the general population in Turkey ranged from 0.47% to 0.55% in children and from 0.39% to 0.70% in adults.[80–83] Similar data were reported from Israel, where a prevalence of serodiagnosis of CeD of 0.7% (95% CI, 0.24%–1.02%) was found in adults.[84] In Egypt, a serologic screening conducted in the pediatric general population (n = 1500, age 7 months through 18 years) demonstrated a prevalence of 0.53% (95% CI, 0.17%–0.89%) and 6.4% (95% CI, 3.4%–9.4%) in children with type 1 diabetes.[85]

Furthermore, recent data from Israel suggest a rise in the incidence of CeD autoimmunity between 2007 and 2015. In the large population covered by the Maccabi Healthcare Service (the second largest health maintenance organization in Israel, ensuring 2.3 million members, 25% of the Israelian population), the incidence of CeD autoimmunity (based on TTG IgA antibodies) increased from 25.4 per 100,000 in 2007 to 52.3 per 100,000 person-years in 2015 (incidence rate ratio, 2.06; 95% CI, 1.81–2.26). Increasing incidence was highest in small children (0–5 years), whereas the incidence in adults was stable.[86]

Central Asia and Russia

Although the carrier frequency of HLA-DQ2/DQ8 haplotypes in the Russian population, especially in the Western region, is comparable with that in Europe, there is a lack of systematic studies from central Asia and Russia. Summarizing the review of literature, Savvateeva et al[87] reported an increase in the prevalence of CeD in children during the last few decades and at least 0.6% of them have CeD.

The Asian "Iceberg" of Celiac Disease

There is a lack of studies from Asian countries describing the incidence of CeD. Summarizing the prevalence studies from Asian regions, a recent systemic review and meta-analysis found the pooled seroprevalence and prevalence of biopsy-confirmed CeD in low-risk groups to be 1.2% and 0.61%, respectively.[88]

Although both the incidence and prevalence of CeD are increasing, most patients with CeD globally remain undiagnosed, more so in Asian countries. Although wheat has not been a staple cereal for many ethnic groups, such as in Japan, Malaysia, Indonesia, or the Southern part of India, wheat is becoming popular in these nations because of its use in convenience foods and fast foods. Hence, CeD may emerge in many of these nations and we should be watchful for this. Even if there are patients with CeD, they are not diagnosed because of strong beliefs of its nonoccurrence in their regions and even when clinical suspicion exists about CeD, nonavailability of diagnostic infrastructure becomes a barrier in many Asian countries.[89] Therefore, there is a need to increase awareness about CeD in countries where CeD is still considered to be uncommon.

Oceania

Data from Oceania are mostly restricted to Australia. In the year 2001, the retrospective analysis of stored serum samples (collected in 1994–1995) from 3011 random subjects from the Busselton Health Study (South-West Australia) found a CeD prevalence of 0.4%, including both EMA-positive patients and those previously diagnosed, with clustering of cases in the age range from 30 through 50 years.[90] Years later, Anderson and coworkers,[91] by screening with TTG IgA antibodies, EMAs, and HLA-DQ genetic testing, found that the prevalence of CeD in a sample of 2548 adults randomly sampled in Barwon, New South Wales had increased to at least 1.1% in men and 1.0% in women, therefore, mirroring the trend toward increasing frequency observed in Europe and United States. Finally, a recent "opportunistic" TTG IgA antibodies and deamidated gliadin IgG–based screening was performed on 1055 patients presenting to a children's hospital emergency department in Sydney for undifferentiated acute care. The prevalence of biopsy-confirmed CeD was 0.7% (7 of 1055), including 2 new diagnoses and 5 subjects with known CeD.[92] Opportunistic CeD screening is an intermediate policy between mass screening and case finding that could find wider application for CeD case detection.

Burden of Celiac Disease: The Patient and the Community Perspectives

The concept of burden was introduced to quantify the impact of a disease at both patient and community levels. The disease burden can be assessed by means of epidemiologic (prevalence and incidence), clinical (morbidity and mortality), health utility (eg, quality-adjusted life-years), and economic (direct and indirect costs) indicators.[93] As we have detailed, CeD is not only one of the most common permanent disorders in most areas of the world, it goes undetected frequently. For these reasons, consideration of CeD burden, particularly of undetected cases (the "invisible part of the celiac iceberg"), has received increasing attention.

From the patient's perspective, undiagnosed disease is the cause of direct morbidity, including intestinal and extra-intestinal manifestations. The delay in diagnosis may reach 10–13 years or more, and this may cause significant and prolonged impairments in quality of life.[93] Many screening-detected adults with CeD appear to consider their nonspecific symptoms, for example, fatigue or headache, a part of their normal state. Even in these apparently "silent" cases, starting a gluten-free diet (GFD) may result in significant improvements in overall gastrointestinal function and health-related quality of life, with improved levels of energy.[43] Undetected CeD may be responsible for long-term complications, such as infertility, osteoporosis, and cancer, particularly gut lymphoma and small bowel carcinoma.[1] A negative impact of active CeD on bone health has been reported, with an increased risk of osteoporosis and osteoporotic fractures.[94,95] Due to the scarcity of long-term prospective studies, the quantification of the other risks is still uncertain. Even more complex to ascertain is the relationship between untreated CeD and overall mortality, which was increased in some studies[96,97] but not in others.[98,99] Unfortunately, no data are available on the possible role of untreated CeD as a cause of diarrhea- or malnutrition-associated mortality, particularly in children, in low-income countries.

The burden related to treatment of CeD deserves consideration as well. The GFD is a safe intervention that allows remission of the disease. However, studies have shown deficient intake of some nutrients over the long run, particularly fiber, calcium, iron, folate, and other vitamins. Although commercial GF items may contain more simple sugars and fat than normal products, most studies have not documented an increased risk of obesity or dyslipidemia.[1] Undiagnosed CeD causes a substantial decrement in

quality of life that improves after starting treatment with the GFD.[100] However, the need to avoid staple and enjoyable wheat-based food forever may be perceived as a high treatment burden in comparison with other chronic illnesses.[101] The need to constantly pay attention to the diet may be responsible for psychological disturbances, particularly during vulnerable periods, such as adolescence.[1] Social and structural barriers to maintaining the GFD may be challenging in countries with poor CeD awareness, for example, China.[102] However, most studies to date have not confirmed a negative impact of CeD treatment on health-related quality of life and GFD adherence.[103] The treatment-related burden is lower in patients diagnosed early in childhood,[104] in males, and in countries with greater CeD awareness and availability of GF food, and might decrease in the near future as soon as alternative or complementary treatments to the GFD become available.

From the community perspective, only a few studies investigated the costs associated with CeD. A US study evaluated total inpatient and outpatient costs for those with CeD and those without, and concluded that diagnosis of CeD is associated with a reduction in medical costs, but that outpatient costs and total costs were higher in individuals with CeD compared with controls.[105] A Swedish study analyzed the cost-effectiveness of a CeD mass screening at 12 years of age, taking a life-course perspective on future benefits and drawbacks. The cost for CeD screening was EUR 40,105 per gained quality-adjusted life-year. Authors concluded that CeD mass screening is cost-effective based on the commonly used threshold of EUR 50,000 per gained quality-adjusted life-year, however, this estimate was based on many assumptions, especially regarding the natural history of CeD.[106] GF products are generally more expensive than their wheat-based counterparts, an aspect that should be included in the evaluation of the economic burden of CeD, from both the patient and community perspectives. A recent US study found that GF products were more expensive (overall 183%) in all regions and venues with a trend of decreasing costs over time (240% in the year 2006).[107] The additional costs of GF food are charged only to the patient in many countries, while in others they may be covered, at least in part, by the local health system or insurance.

The burden of undetected CeD is heavy from both the patient and the community perspectives (Figure 2), particularly in areas with high disease prevalence and poor disease awareness. Although treatment of CeD carries its own burden, the advantages of CeD recognition appear overwhelming (Figure 2). Due to the lack of efficient strategies for primary prevention of CeD, early diagnosis (secondary prevention) currently represents the only way to reduce the impact of CeD at the population level.

How to Improve the Celiac Disease Detection Rate: Case Finding vs Mass Screening

As discussed previously, one of the main challenges for CeD worldwide is that most cases of CeD remain undiagnosed and patients are consequently exposed to the risk of long-term complications, even in countries with a high level of CeD awareness.[43] How to improve the CeD diagnostic rate is still a matter of debate. International gastroenterology societies unanimously recommend a case-finding policy, such as testing subjects belonging to at-risk groups (eg, relatives of patients with CeD and subjects with chronic intestinal symptoms or who are IgA-deficient).[38,108,109] Case finding is ethically sound, and inexpensive. However, this policy is poorly efficient and requires testing >50% of the general population if implemented in a proactive manner.[110]

Pediatric screening is highly sensitive and allows the detection and early treatment of most CeD cases.[39] CeD satisfies most of the criteria defined by the World Health Organization (so-called Wilson and Jungner criteria) for screening, for example (1) the condition sought should be an important health problem, (2) there should be a recognizable preclinical stage, (3) there should be a suitable and acceptable test, and (4) there should be an accepted treatment for patients with recognized disease.[111] Despite some unanswered questions, that is, how to follow-up screening-negative subjects, CeD mass screening is gaining increasing attention within the scientific community. Pilot studies, such as the ASK (Autoimmunity Screening for Kids) project implemented by the Barbara Davis Center at the University of Colorado, are currently in progress to evaluate the feasibility and efficiency of CeD mass screening coupled with the screening of stage 1 type 1 diabetes in children.[112] On September 17, 2023, the Italian Parliament took a step forward when they approved a law (Italian Republic Law 130, 2023) introducing a nationwide screening for type 1 diabetes and CeD in the general population aged 1–17 years as part of the public health programs ultimately aimed at reducing the impact of these chronic diseases.[113]

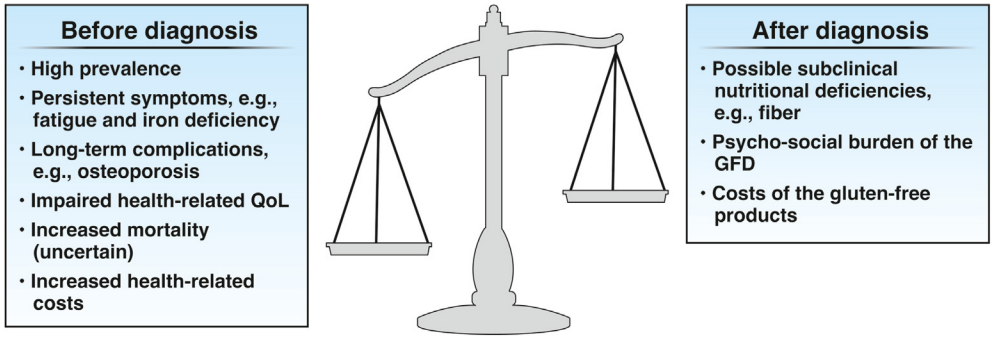

Figure 2. The burden of celiac disease, particularly related to cases that remain undetected unless actively searched by population screening. QoL, quality of life.

In summary, case finding is currently the internationally agreed upon policy for CeD identification. However, pediatric screening seems to be the road ahead for thorough CeD detection, at least in countries with an efficient health care system.

Conclusions

In most areas of the world, CeD is one of the most common life-long disorders, with a prevalence of approximately 1%–2% in the general population. Consequently, the patient and community CeD-related health global burden is heavy, particularly for females. The reasons for such a huge diffusion of CeD are still unclear, but could be related, at least in part, to the general increase in autoimmune diseases. Another factor potentially responsible for the increasing burden of CeD worldwide is the growing diffusion of wheat-based convenience food, such as burger and pizza, in areas traditionally characterized by a low-gluten diet, such as Eastern Asia and Central America. Despite a significant increase in the incidence of clinically diagnosed CeD, still a significant proportion of cases (>50% in most countries) remains undiagnosed. There is a need to increase awareness about CeD in countries where CeD is still considered to be uncommon, particularly in many Asian areas.

The burden of CeD is variable and the challenges by region or country are at different stages of complexity (eg, need for longitudinal care due to higher detection of cases in high-income countries vs need for better awareness and availability of serology tests in other countries). Although treatment of CeD carries its own burden, particularly related to the psychosocial consequences of the GFD, the advantages of early CeD recognition appear overwhelming. A careful policy of systematic case finding is currently considered the best buy for improving the CeD detection rate; however, this policy has significant limitations. Pediatric screening of the general population could represent the road ahead for an efficient intervention of secondary prevention aimed to reduce the health and social burden of CeD.

References

1. Catassi C, Verdu EF, Bai JC, et al. Coeliac disease. Lancet 2022;399:2413–2426.
2. Rubio-Tapia A, Ludvigsson JF, Brantner TL, et al. The prevalence of celiac disease in the United States. Am J Gastroenterol 2012;107:1538–1544.
3. Ludvigsson JF, Rubio-Tapia A, van Dyke CT, et al. Increasing incidence of celiac disease in a North American population. Am J Gastroenterol 2013;108:818–824.
4. Choung RS, Unalp-Arida A, Ruhl CE, et al. Less hidden celiac disease but increased gluten avoidance without a diagnosis in the United States: findings from the National Health and Nutrition Examination Surveys from 2009 to 2014. Mayo Clin Proc 2017;92:30–38.
5. Unalp-Arida A, Ruhl CE, Choung RS, et al. Lower prevalence of celiac disease and gluten-related disorders in persons living in southern vs northern latitudes of the United States. Gastroenterology 2017;152:1922–1932.e2.
6. Celdir MG, Jansson-Knodell CL, Hujoel IA, et al. Latitude and celiac disease prevalence: a meta-analysis and meta-regression. Clin Gastroenterol Hepatol 2022;6:e1231–e1239.
7. Zylberberg HM, Miller EBP, Ratner A, et al. Correlations between relative prevalence of celiac disease and sociodemographic variables in the United States. Am J Gastroenterol 2024;119:374–377.
8. Stahl M, Li Q, Lynch K, et al. Incidence of pediatric celiac disease varies by region. Am J Gastroenterol 2023;118:539–545.
9. Ching CK, Lebwohl B. Celiac disease in the elderly. Curr Treat Options Gastroenterol 2022;20:238–249.
10. Freeman HJ. Detection of adult celiac disease with duodenal screening biopsies over a 30-year period. Can J Gastroenterol 2013;27:405–408.
11. King JA, Bakal JA, Li B, et al. Variation in testing for and incidence of celiac autoimmunity in Canada: a population-based study. Gastroenterology 2023;164:567–578.e7.
12. King JA, Jeong J, Underwood FE, et al. Incidence of celiac disease is increasing over time: a systematic review and meta-analysis. Am J Gastroenterol 2020;115:507–525.
13. Chan J, Mack DR, Manuel DG, et al. Validation of an algorithm to identify children with biopsy-proven celiac disease from within health administrative data: an assessment of health services utilization patterns in Ontario, Canada. PLoS One 2017;12:e0180338.
14. 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.
15. Remes-Troche JM, Nuñez-Alvares C, Uscanga-Dominguez LF. Celiac disease in Mexican population: an update. Am J Gastroenterol 2013;108:283–284.
16. Peña AS, Crusius JB. Central America in transition: from maize to wheat challenges and opportunities. Nutrients 2015;7:7163–7171.
17. Gomez JC, Selvaggio GS, Viola M, et al. Prevalence of celiac disease in Argentina: screening of an adult population in the La Plata area. Am J Gastroenterol 2000;96:2700–2704.
18. Gomez JC, Selvaggio G, Pizarro B, et al. Value of a screening algorithm for celiac disease using tissue transglutaminase antibodies as first level in a population-based study. Am J Gastroenterol 2002;97:2785–2790.
19. Mora M, Litwin N, Toca Mdel 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.
20. Vázquez H, de la Paz Temprano M, 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.

21. 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 (Sao Paulo) 2012;67:1013–1018.
22. 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.
23. 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.
24. Oliveira LC, Dornelles AC, Nisihara RM, et al. The second highest prevalence of celiac disease worldwide: genetic and metabolic insights in southern Brazilian Mennonites. Genes (Basel) 2023;14:1026.
25. Paredes-Echeverri S, Rodríguez AN, Cárdenas WA, et al. Seroprevalence of antitransglutaminase and anti-endomysium antibodies in adult Colombian blood bank donors. Can J Gastroenterol Hepatol 2020:7541941.
26. 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.
27. Baldera K, Chaupis-Meza D, Cárcamo C, et al. Population seroprevalence of celiac disease in urban areas of Peru. Rev Peru Med Exp Salud Publica 2020;37:63–66.
28. von Mühlenbrock-Pinto C, Madrid-Silva AM. Celiac disease in Chilean adults. Rev Gastroenterol Mex 2023; 88:28–35.
29. Parada A, Méndez C, Espino A, et al. Adherence to a gluten-free diet and quality of life in Chilean celiac patients. Rev Esp Enferm Dig 2021;113:429–431.
30. Méndez C, Carrasco M, Mora B, et al. Caracterización de la enfermedad celiaca en niños atendidos en hospitales públicos chilenos [Characterization of celiac disease in Chilean public hospitals]. Rev Chil Pediatr 2018; 89:709–717.
31. Fernández-Mestre M, Padrón-Lowe D, Salazar-Alcalá E, et al. Role of HLA-DQB1 alleles in the risk, signs and symptoms, and severity of celiac disease in a Venezuelan population. Rev Gastroenterol Mex 2023; 88:125–131.
32. Holmes GKT, Muirhead A. Epidemiology of coeliac disease in a single centre in Southern Derbyshire 1958-2014. BMJ Open Gastroenterol 2017;4:e000137.
33. Bergman D, King J, Lebwohl B, et al. Two waves of coeliac disease incidence in Sweden: a nationwide population-based cohort study from 1990 to 2015. Gut 2022;71:1088–1094.
34. Roberts SE, Morrison-Rees S, Thapar N, et al. Systematic review and meta-analysis: the incidence and prevalence of paediatric coeliac disease across Europe. Aliment Pharmacol Ther 2021;54:109–128.
35. Catassi C, Rätsch IM, Fabiani E, et al. Coeliac disease in the year 2000: exploring the iceberg. Lancet 1994; 343:200–203.
36. Grodzinsky E, Franzen L, Hed J, et al. High prevalence of celiac disease in healthy adults revealed by antigliadin antibodies. Ann Allergy 1992;69:66–70.
37. 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.
38. Husby S, Koletzko S, Korponay-Szabó I, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for diagnosing coeliac disease 2020. J Pediatr Gastroenterol Nutr 2020;70:141–156.
39. Lionetti E, Pjetraj D, Gatti S, et al. Prevalence and detection rate of celiac disease in Italy: results of a SIGENP multicenter screening in school-age children. Dig Liver Dis 2023;55:1328–1337.
40. Gatti S, Lionetti E, Balanzoni L, et al. Increased prevalence of celiac disease in school-age children in Italy. Clin Gastroenterol Hepatol 2020;18:596–603.
41. Ivarsson A, Myléus A, Norström F, et al. Prevalence of childhood celiac disease and changes in infant feeding. Pediatrics 2013;131:e687–e694.
42. Björck S, Brundin C, Lörinc E, et al. Screening detects a high proportion of celiac disease in young HLA-genotyped children. J Pediatr Gastroenterol Nutr 2010; 50:49–53.
43. Kvamme JM, Sørbye S, Florholmen J, et al. Population-based screening for celiac disease reveals that the majority of patients are undiagnosed and improve on a gluten-free diet. Sci Rep 2022;12:12647.
44. 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.
45. Jansen M, van Zelm M, Groeneweg M, et al. The identification of celiac disease in asymptomatic children: the Generation R Study. J Gastroenterol 2018;53:377–386.
46. Fernández-Fernández S, Borrell B, Cilleruelo ML, et al. Prevalence of celiac disease in a long-term study of a Spanish at-genetic-risk cohort from the general population. J Pediatr Gastroenterol Nutr 2019;68:364–370.
47. Taavela J, Kurppa K, Jääskeläinen T, et al. Trends in the prevalence rates and predictive factors of coeliac disease: a long-term nationwide follow-up study. Aliment Pharmacol Ther 2024;59:372–379.
48. Catassi C, Kryszak D, Bhatti B, et al. Natural history of celiac disease autoimmunity in a USA cohort followed since 1974. Ann Med 2010;42:530–538.
49. Choung RS, Larson SA, Khaleghi S, et al. Prevalence and morbidity of undiagnosed celiac disease from a community-based study. Gastroenterology 2017; 152:830–839.e5.
50. Crawley C, Sander SD, Nohr EA, et al. High prevalence of celiac disease among Danish adolescents: a population-based study. J Pediatr Gastroenterol Nutr 2022;74:85–90.
51. Horwitz A, Skaaby T, Kårhus LL, et al. Screening for celiac disease in Danish adults. Scand J Gastroenterol 2015;50:824–831.
52. Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018;16:823–836.e2.
53. Catassi C, Rätsch IM, Gandolfi L, et al. Why is coeliac disease endemic in the people of the Sahara? Lancet 1999;354:647–648.

54. Teresi S, Crapisi M, Vallejo MD, et al. Celiac disease seropositivity in Saharawi children: a follow-up and family study. J Pediatr Gastroenterol Nutr 2010; 50:506–509.
55. 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.
56. Catassi C, Doloretta Macis M, et al. The distribution of DQ genes in the Saharawi population provides only a partial explanation for the high celiac disease prevalence. Tissue Antigens 2001;58:402–406.
57. 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.
58. Bdioui F, Sakly N, Hassine M, et al. Prevalence of celiac disease in Tunisian blood donors. Gastroenterol Clin Biol 2006;30:33–36.
59. Ben Hariz M, Kallel-Sellami M, Kallel L, et al. Prevalence of celiac disease in Tunisia: mass-screening study in schoolchildren. Eur J Gastroenterol Hepatol 2007; 19:687–694.
60. 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.
61. Ageep AK. Celiac disease in the Red Sea state of Sudan. Trop Gastroenterol 2012;33:118–122.
62. Ibaid I, Hussien M, Kaukinen K, et al. Role of HLA-DQ typing and antitissue transglutaminase antibody titres in diagnosing coeliac disease among Sudanese children with type 1 diabetes mellitus. BMJ Open Gastroenterol 2022;9:e000735.
63. National Geographic. Asia: Human Geography. Available at: https://education.nationalgeographic.org/resource/asia-human/. Accessed October 14, 2023.
64. Makharia GK, Catassi C. Celiac disease in Asia. Gastroenterol Clin North Am 2019;48:101–113.
65. Sood A, Midha V, Sood N, et al. Prevalence of celiac disease among school children in Punjab, North India. J Gastroenterol Hepatol 2006;21:1622–1625.
66. Makharia GK, Verma AK, Amarchand R, et al. Prevalence of celiac disease in the northern part of India: a community based study: celiac disease in India. J Gastroenterol Hepatol 2011;26:894–900.
67. 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.
68. Zanella S, De Leo L, Nguyen-Ngoc-Quynh L, et al. Cross-sectional study of coeliac autoimmunity in a population of Vietnamese children. BMJ Open 2016;6: e011173.
69. Yap TWC, Chan WK, Leow AHR, 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.
70. Yuan J, Gao J, Li X, et al. The tip of the "celiac iceberg" in China: a systematic review and meta-analysis. PLoS One 2013;8:e81151.
71. Yuan J, Zhou C, Gao J, et al. Prevalence of celiac disease autoimmunity among adolescents and young adults in China. Clin Gastroenterol Hepatol 2017; 15:1572–1579.e1.
72. Zhou C, Gao F, Gao J, et al. Prevalence of coeliac disease in Northwest China: heterogeneity across Northern Silk road ethnic populations. Aliment Pharmacol Ther 2020;51:1116–1129.
73. Kou GJ, Guo J, Zuo XL, et al. Prevalence of celiac disease in adult Chinese patients with diarrhea-predominant irritable bowel syndrome: a prospective, controlled, cohort study. J Dig Dis 2018;19:136–143.
74. Zhou WY, Liu XY, Wang MM, et al. Prevalence of celiac disease in China: meta-analysis and serological survey in high-risk populations. J Dig Dis 2021; 22:645–655.
75. Hokari R, Higashiyama M. Extremely low prevalence of celiac disease in Japan: eternal silence or just the calm before the storm? JGH Open 2020;4:554–555.
76. Fukunaga M, Ishimura N, Fukuyama C, et al. Celiac disease in non-clinical populations of Japan. J Gastroenterol 2018;53:208–214.
77. El-Metwally A, Toivola P, AlAhmary K, et al. The epidemiology of celiac disease in the general population and high-risk groups in Arab countries: a systematic review. Biomed Res Int 2020;2020:1–13.
78. Mohammadibakhsh R, Sohrabi R, Salemi M, et al. Celiac disease in Iran: a systematic review and meta-analysis. Electron Physician 2017;9:3883–3895.
79. Barada K, Habib RH, Malli A, et al. Prediction of celiac disease at endoscopy. Endoscopy 2014;46:110–119.
80. Ertekin V, Selimoglu MA, Kardas F, et al. Prevalence of celiac disease in Turkish children. J Clin Gastroenterol 2005;39:689–691.
81. Dalgic B, Sari S, Basturk B, et al. Prevalence of celiac disease in healthy Turkish school children. Am J Gastroenterol 2011;106:1512–1517.
82. 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.
83. Sezgin O, Saritaş B, Aydin I, et al. Celiac disease prevalence in Turkey: a population based cross-sectional study. Acta Med Mediterr 2016;32:719–727.
84. 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.
85. 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.
86. Lechtman N, Shamir R, Cohen S, et al. Increased incidence of coeliac disease autoimmunity rate in Israel: a 9-year analysis of population-based data. Aliment Pharmacol Ther 2021;53:696–703.
87. Savvateeva LV, Erdes SI, Antishin AS, et al. Overview of celiac disease in Russia: regional data and estimated prevalence. J Immunol Res 2017:2314813.
88. Ashtari S, Najafimehr H, Pourhoseingholi MA, et al. Prevalence of celiac disease in low and high-risk

population in Asia-Pacific region: a systematic review and meta-analysis. Sci Rep 2021;11:2383.
89. Makharia GK, Singh P, Catassi C, et al. The global burden of coeliac disease: opportunities and challenges. Nat Rev Gastroenterol Hepatol 2022;19:313–327.
90. 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.
91. Anderson RP, Henry MJ, Taylor R, et al. A novel serogenetic approach determines the community prevalence of celiac disease and informs improved diagnostic pathways. BMC Med 2013;11:188.
92. Pathmanandavel K, Wong M, Williams E, et al. Opportunistic coeliac disease screening in undifferentiated presentations to paediatric acute care. J Paediatr Child Health 2023;59:992–997.
93. Mogul D, Nakamura Y, Seo J, et al. The unknown burden and cost of celiac disease in the U.S. Expert Rev Pharmacoecon Outcomes Res 2017;17:181–188.
94. Hujoel IA, Van Dyke CT, Brantner T, et al. Natural history and clinical detection of undiagnosed coeliac disease in a North American community. Aliment Pharmacol Ther 2018;47:1358–1366.
95. Hansen S, Schwarz P, Rumessen J, et al. Osteoporosis and bone fractures in patients with celiac disease: a nationwide cohort study. Bone 2023;177:116913.
96. Rubio-Tapia A, Kyle RA, Kaplan EL, et al. Increased prevalence and mortality in undiagnosed celiac disease. Gastroenterology 2009;137:88–93.
97. Lebwohl B, Green PHR, Söderling J, et al. Association between celiac disease and mortality risk in a Swedish population. JAMA 2020;323:1277–1285.
98. Kårhus LL, Skaaby T, Petersen J, et al. Long-term consequences of undiagnosed celiac seropositivity. Am J Gastroenterol 2020;115:1681–1688.
99. Canavan C, Logan RF, Khaw KT, et al. No difference in mortality in undetected coeliac disease compared with the general population: a UK cohort study. Aliment Pharmacol Ther 2011;34:1012–1019.
100. Violato M, Gray A. The impact of diagnosis on health-related quality of life in people with coeliac disease: a UK population-based longitudinal perspective. BMC Gastroenterol 2019;19:68.
101. Shah S, Akbari M, Vanga R, et al. Patient perception of treatment burden is high in celiac disease compared with other common conditions. Am J Gastroenterol 2014;109:1304–1311.
102. Zhang Q, Wolf RL, Lee AR, et al. Navigating celiac disease and the gluten-free diet in China. Nutr Health 2021;27:395–403.
103. Shuler B, Liu E, Stahl MG. Population level screening for celiac disease: is now the time? Curr Opin Gastroenterol 2023;39:455–462.
104. Nikniaz Z, Abbasalizad Farhangi M, Nikniaz L. Systematic review with meta-analysis of the health-related quality of life in children with celiac disease. J Pediatr Gastroenterol Nutr 2020;70:468–477.
105. Long KH, Rubio-Tapia A, Wagie AE, et al. The economics of coeliac disease: a population-based study. Aliment Pharmacol Ther 2010;32:261–269.
106. Norström F, Myléus A, Nordyke K, et al. Mass screening for coeliac disease a wise use of resources? A health economic evaluation. BMC Gastroenterol 2021;21:159.
107. Lee AR, Wolf RL, Lebwohl B, et al. Persistent economic burden of the gluten free diet. Nutrients 2019;11:399.
108. Ludvigsson JF, Bai JC, Biagi F, et al. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. Gut 2014;63:1210–1228.
109. Rubio-Tapia A, Hill I, Semrad C, et al. American College of Gastroenterology Guidelines update: diagnosis and management of celiac disease. Am J Gastroenterol 2023;118:59–76.
110. Catassi GN, Pjetraj D, Gatti S, et al. Celiac disease detection strategies: poor performance of the case-finding policy. Am J Gastroenterol 2023;118:1702–1703.
111. Wilson J, Jungner G. Principles and Practice of Screening for Disease. World Health Organization, 1968.
112. Stahl MG, Geno Rasmussen C, Dong F, et al. Mass screening for celiac disease: the Autoimmunity Screening for Kids Study. Am J Gastroenterol 2021;116:180–187.
113. Bosi E, Catassi C. Screening type 1 diabetes and celiac disease by law: a novel challenging strategy from Italy. Lancet Diab Endocrinol 2024;12:12–14.

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Conflicts of interest
The authors disclose no conflicts.