

# Review article: Epidemiology of coeliac disease

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## Summary

Coeliac disease is an immune-mediated disease caused by ingestion of gluten in genetically susceptible individuals. Coeliac disease has been thought to affect mainly people of European origin but subsequently many studies revealed that it affects people living in North America, Oceania, South America, Asia as well as Africa. The global pooled seroprevalence and prevalence of biopsy-confirmed coeliac disease are 1.4% and 0.7% respectively. The pooled incidence rates in women and men are 17.4 (95% CI: 13.7-21.1) and 7.8 (95% CI: 6.3-9.2) per 100 000 person-years respectively. The systematic reviews, based on many population-based data, suggest that both the prevalence and the incidence of coeliac disease has increased over past three decades, which may be attributable not only to an increase in the detection rate (improvement in diagnostic tests, simplification of diagnostic criteria and increase in awareness about the disease) but also because of modernisation and globalisation related changes in the dietary practices including increase in the use of convenience food and dietary gluten. In addition to genetic factors, while there are many environmental risk factors, including age at the first introduction of gluten, breastfeeding, caesarean section, exposure to antibiotics and gut microbiome; the amount of gluten ingestion during early part of life, however, has been shown to increase the risk of coeliac disease, and this is relevant from the point of view of primary prevention. In this review, we have reviewed and summarised the literature, up till year 2021, related to the global and continent-wise epidemiology and risk factors associated with coeliac disease.

## 1 | INTRODUCTION

Coeliac disease (CD) occurs because of interaction between both environmental (gluten) and genetic factors (HLA and non-HLA genes), and the distribution of these two components can guide to identify the areas of the world at risk for CD.<sup>1</sup> During the very early part of the evolution, men led a nomadic life and obtained food by hunting, fishing and collecting fruits and vegetables. Therefore, we can infer that CD did not exist during the Palaeolithic age, as the diet of hunter-gatherers consisted of only meat, vegetables and fruits, and was gluten free by its origin.

About 10,000 years ago in a region of South Western Asia, called the "Fertile Crescent" including Southern Turkey, Lebanon, Syria, Palestine and Iraq, the local community started cultivating wild grains due to the special environmental conditions created by the flooding. In the Fertile Crescent, some tribes changed their lifestyle from nomadic to a stable settlement because land cultivation permitted them to store food.<sup>2</sup> The first wheat varieties, that were successfully domesticated, were Einkorn and Emmer wheat.<sup>3</sup> The progressive spread of agriculture from the East to Europe stimulated the population growth (as a result of the increasing availability of food) and local migratory activity.<sup>4</sup> While there might have been patients with CD after the cultivation started, CD, was originally described in 19th century principally in children by Samuel Gee in England and by Christian Herter in

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the United States. Until the mid-20th century, CD was known as Gee-Herter disease. In the modern era, the population migration is rather rapid and there is a constant mixing of different ethnic groups all over the world.<sup>2,5,6</sup>

The journey of CD from its first description by Samuel Gee to a great breakthrough discovery of wheat being its cause, based on diligent clinical observation and clinical enquiry of five young patients, by Willem Karel Dicke has been very inspiring.<sup>7,8</sup> CD is a unique disease in the sense that the treatment of the disease has been discovered decades before understanding or unravelling of its pathophysiology. While the introduction of gastrointestinal endoscopic techniques in 1970s for taking biopsies from the intestinal mucosa and identification of two human leucocyte antigen (HLA) molecules (HLA-DQ2 and HLA-DQ8) in late 1980s led to the understanding of the pathology and pathophysiology of CeD, the discovery of serologic tests such as anti-endomysial antibody (EMA), anti-tissue transglutaminase antibody (IgA tTG Ab) or anti-deamidated gliadin peptide antibody (anti-DGP Ab) has not only allowed screening of high-risk group for CD, but also made it possible to estimate its true prevalence in the general population.<sup>9-14</sup>

## 2 | GLOBAL EPIDEMIOLOGY OF CeD

### 2.1 | Epidemiology of CeD

Initial epidemiological studies conducted in 1950, when the diagnosis of CD was based entirely on the presence of typical gastrointestinal symptoms, showed a cumulative prevalence of 1 in 8000 in England and 1 in 4000 in Scotland.<sup>15</sup> With the availability of more specific tests for malabsorption, advent of Crosby capsule for intestinal biopsies, and an increase in awareness about CD, the prevalence of CD increased in 1970s to 1 in 450 in Ireland, Scotland and Switzerland.<sup>16,17</sup>

### 2.2 | Modern epidemiology of CD

The foundation of modern era of epidemiology of CD was laid in 1996 in Italy when Catassi et al.<sup>18</sup> reported the results of a large population-based serological screening of 17 201 healthy Italian schoolchildren aged 6-15 years. This study brought two important facts: first, the prevalence of undiagnosed CD was 4.7/1000 (95% CI 3.7-5.9), that is, 1 in 210 subjects. Second, the overall prevalence of CD, including those who were already diagnosed with CD earlier, was 5.4/1000 (95% CI 4.5-6.4), that is, 1 in 184 subjects. More interestingly, only one in seven was diagnosed previously as CD, suggesting that a larger number of subjects remained clinically undiagnosed. This landmark serology-based study catalysed the exploration of epidemiology of CD in different parts of the world.

### 2.3 | The global burden of CD

A real-time assessment of the prevalence of CD is denoted via seroprevalence (proportion of people having a positive anti-tTG Ab and/or anti-endomysial Ab) and prevalence of biopsy-confirmed CD (proportion of individuals with villous abnormalities of modified Marsh grade 2 or more along with a positive serological test).

#### 2.3.1 | Global seroprevalence of CD

A systematic review and meta-analysis of population-based studies, including 275 818 subjects has shown that the pooled global seroprevalence of CD in the general population is 1.4% (95% CI 1.1%-1.7%).<sup>19</sup> The seroprevalence varies from continent to continent, and the highest seroprevalence has been reported in the Europe and the Asia (Table 1). Furthermore, the seroprevalence also varies from country to country, the highest being in Algeria, Czech Republic, India, Israel, Mexico, Saudi Arabia, Sweden, Portugal and Turkey and lowest in Estonia, Germany, Iceland, Libya, Poland, Republic of San Marino and Spain.<sup>19</sup>

#### 2.3.2 | Global prevalence of biopsy-confirmed CD

The same systematic review and meta-analysis of population-based studies has further shown that the global pooled prevalence of biopsy-confirmed CD is 0.7% (95% CI 0.5%-0.9%).<sup>19</sup> On stratification of countries into quintiles based on the prevalence of biopsy-confirmed CD, countries with the highest prevalence (76-100th quintile) are Argentina, Egypt, Hungary, Finland, India, New Zealand and Sweden; and the countries with the lowest prevalence (0-25th quintile) include Brazil, Germany, Republic of San Marino, Russia and Tunisia.

Most population-based epidemiological studies to assess the prevalence of CD are based on a positive coeliac serological test, and the diagnosis in all seropositive patients has not been confirmed by intestinal mucosal biopsies, which likely is the explanation of the differences in the population-based seroprevalence and prevalence of biopsy-confirmed CD.<sup>19-22</sup> Therefore, the estimated prevalence based on prevalence of biopsy-confirmed CD may be an underestimation of the true prevalence. Furthermore, the population-based prevalence data are still not available from many countries and thus the presently observed prevalence data may not reflect the real global prevalence of CD.

## 2.4 | Continent-wise prevalence of CD

### 2.4.1 | Prevalence of CD in Europe

Most of the initial studies on the prevalence of CD were from European countries such as Italy, the United Kingdom and Finland.

**TABLE 1** Prevalence and incidence of coeliac disease

Incidence and prevalence	Seroprevalence	Prevalence of Biopsy-confirmed coeliac disease
Prevalence		
Global <sup>a</sup>	1.4% (95% CI 1.1-1.7)	0.7% (95% CI 0.5-0.9)
Continent wise		
Europe	1.3 (95% CI 1.1-1.5) <sup>a</sup>	0.8(95% CI 0.6-1.1) <sup>a</sup> 0.74 <sup>b</sup> (In children and adolescence)
North America <sup>a</sup>	1.4 (95% CI 0.7-2.2)	0.5
South America <sup>a</sup>	1.3 (95% CI 0.5-2.5)	0.4 (95% CI 0.1-0.6)
Africa <sup>a</sup>	1.1 (95% CI 0.4-2.2)	0.5 (95% CI 0.2-0.9)
Asia <sup>c</sup>	1.2 (95% CI 0.8-1.7)	0.61 (95% CI 0.4-0.8)
Oceania <sup>a</sup>	1.4 (95% CI 1.4-1.8)	0.8 (95% CI 0.2-1.7) 0.6(95% CI 0.001-20) <sup>bh</sup>
Incidence rate <sup>d</sup>		
Male	7.8 (95% CI: 6.3-9.2) per 100 000 person-years	
Female	17.4 (95% CI 13.7-21.1) per 100 000 person-years	
Children	21.3 (95% CI: 15.9-26.7) per 100 000 person-years	
Adults	12.9 (95% CI: 7.6-18.2) per 100 000 person-years	

<sup>a</sup>Singh et al<sup>19</sup><sup>b</sup>Roberts et al<sup>24</sup><sup>c</sup>Ashtari et al.<sup>61</sup><sup>d</sup>King et al<sup>82</sup>

In the first multinational European study, 29 212 subjects from Finland, Germany, Italy and the United Kingdom were screened for CD, and the overall prevalence was estimated to be 1.0%.<sup>23</sup> Consistent with this, two recent meta-analyses have estimated the prevalence of biopsy-proven CD in Europe to be around 0.7-0.8%.<sup>19,24</sup> However, a regional variation has been noted with higher prevalence reported from northern Europe (1.6%) compared to eastern (0.98%), southern (0.69%) and western (0.60%) Europe.<sup>24</sup> For example, the prevalence of CD in northern European nations of Sweden, Finland and Denmark is around 2%-3%, much higher than that reported in other European nations.<sup>23,25,26</sup> Several recent studies indicate that the prevalence of CD in various European nations is on the rise. In a recent Italian study of over 4500 children, the prevalence was found to be 1.58% which was significantly higher than the that observed in 1990s.<sup>27</sup> Similarly, a recent German study including 2363 children,<sup>28</sup> the seroprevalence of CD was found to be 1.57%, much higher than the seroprevalence of 0.3%-0.8% reported in previous studies.<sup>29,30</sup>

#### 2.4.2 | Prevalence of CD in America (North America and South America)

Among North American countries, population-based screening studies are available from the United States, Canada and Mexico. While CD has been considered to be an uncommon disease in the United States in earlier decades, based on the results of a population-based

prevalence study Fasano, et al in 2003 reported that 1 in 133 Americans having CD.<sup>20</sup> In a recent study including 22 277 persons aged 6 years or older, who participated in the National Health and Nutrition Examination Survey 2009-2014, the prevalence of CD (based on positive anti-tTG Ab followed by positive AEA) in the United States has been reported to be 0.7% (95% CI, 0.5-0.9%), with 1% (95% CI, 0.7-1.2%) among non-Hispanic whites.<sup>31,32</sup> Although the prevalence appears to have increased fivefold between 1974 and 1989 (see below),<sup>33</sup> Choung et al found a stable prevalence of CD at 0.7% between 2009-2010 and 2013-2014.<sup>32</sup> A recent study in a Canadian general population for the first time reported a seroprevalence of CD to be 0.88%.<sup>34</sup> Finally, the prevalence of CD in a Mexican general population appears to be similar to that in the United States and Canada with a reported prevalence (based on positive anti-tTG Ab followed by AEA positivity) as 0.7%.<sup>35,36</sup> Unfortunately, the population-based studies estimating the prevalence of biopsy-proven CD in general population in Canada and Mexico are lacking and further studies are needed.

CD is well known in those South American countries, such as Brazil and Argentina, that are populated by individuals of European origin.<sup>37</sup> Several large population-based studies from Brazil have reported the prevalence of biopsy-proven CD to be 0.2-0.4%.<sup>38-41</sup> Similarly, the prevalence of biopsy-proven CD of 0.6% was reported in a Argentinian general population.<sup>37</sup> Although large population-based studies estimating the prevalence of biopsy-proven CD are not available from other South American countries, CD has been well reported in high-risk populations from several other South American countries such

as Chile,<sup>42</sup> Colombia<sup>43</sup> and Venezuela.<sup>44</sup> Taken together, a systematic review of the studies from South America, the pooled seroprevalence and prevalence of biopsy-confirmed CD has been reported to be 1.3% (95% 0.5-2.5) (11 studies and 20245 subjects screened) and 0.4% (0.1-0.6) (5 studies and 16 550 subjects) respectively.<sup>19</sup>

### 2.4.3 | Prevalence of CD in Oceania

As in the European countries, a population-based study from Australia including 3011 subjects showed the seroprevalence and prevalence of biopsy-confirmed CD to be 1 in 251 and 1 in 430 respectively.<sup>45</sup> A similar population-based study from New Zealand including 1064 subjects has shown the prevalence to be 1.1%.<sup>46</sup>

### 2.4.4 | Prevalence of CD in Africa

An African population originally living in Western Sahara, the Saharawi of Arab-Berber origin, has been reported to have the highest prevalence of CD in the world. In a study involving 989 Saharawi children, a prevalence has been found to be 5.6%, which is almost five times higher than in most European countries.<sup>47</sup> Postulated reasons for the high prevalence in this population have been attributed to the level of consanguinity in this population, higher frequencies of HLA-DQ2 and -DQ8 genotypes in their general population, and consumption of higher quantity of gluten by them.

Although the data on the prevalence of CD are not available from most of the African countries, a systematic review of available data has suggested that the pooled seroprevalence (7 studies and 15,775 subjects) and prevalence of biopsy-confirmed CD (four studies and 7902 subjects) in African continent are 1.1% (95% CI 0.4-2.2) and 0.5% (95% CI 0.2-0.9) respectively.<sup>19</sup> The prevalence of CeD in a few of the African countries has been reported to be 0.5% in Egypt,<sup>48</sup> 0.8% in Libya<sup>49</sup> and 0.6% in Tunisia.<sup>50</sup> However, there is a lack of data on prevalence from sub-Saharan Africa.

### 2.4.5 | Prevalence of CD in Asia

Asia is a large continent and it is divided geographically into five regions namely South Asia, East Asia, Southeast Asia, Central Asia and Western Asia. Due to the heterogeneity of the population, their genetic makeup, economic conditions and the dietary habits, the epidemiology of CD is different in different parts of Asia. Until recent times, CD has been considered to be a rare disease in Asia and patients presenting with diarrhoea and malabsorption were diagnosed usually as having tropical sprue.<sup>51</sup> After the widespread availability of serological tests, multiple screening studies have been performed in many Asian countries such as Turkey, Iran, Israel, Jordan and India and almost all of them summarily show that CD is not an uncommon disease and it most often remains underdiagnosed in Asia.<sup>52</sup>

#### 4.5.1 | South Asia

Among all the Asian countries, CD is well known in India. It has been recognised mainly in the northern part of India, where wheat is the staple diet and a population-based study including 2879 subjects showed the prevalence to be 1.04% (1 in 96).<sup>21</sup> Later, a pan-India study including 23 331 healthy adults from three different regions of India, showed a regional variation in prevalence. While the age-adjusted seroprevalence of CD in Northern, North-Eastern regions were 1.23%, 0.87%, respectively, it was only 0.10% in the Southern region, showing Northern and Southern region gradients.<sup>53</sup>

#### 4.5.2 | East Asia

The epidemiology of CD in China, the largest country, has not been explored until recent years, except for a small case series. In a cross-sectional study including 19 778 Chinese adolescents and young adults (age 16-25 years) from 27 geographic regions in China has shown that more than 2% (2.19%) of them have at least one of the serological tests positive including 1.8% for IgG anti-DGP Ab and 0.36% for IgA anti-tTG Ab.<sup>54</sup> The prevalence of people with a positive coeliac antibody has been 12 times higher in the Northern provinces, such as Shandong, Shaanxi and Henan, where wheat is the staple diet.<sup>54</sup> In another recent study, including 2277 in-patients with gastrointestinal symptoms in four major ethnic groups of Xinjiang Uyghur Autonomous Region of China, the seroprevalence and prevalence of biopsy-confirmed CD have been reported to be 1.27% (95% CI, 0.81%-1.73%) and 0.35% (95% CI, 0.11%-0.59%) respectively.<sup>55</sup> Interestingly, among 246 patients with diarrhoea-predominant irritable bowel syndrome in China, 2.85% were reported to have CD.<sup>56</sup>

In another study from Guangdong Province, China, Zhou et al screened 1390 high-risk population of CeD and observed that 13 of 1390 (0.94) individuals were seropositive for CD.<sup>47</sup> They also conducted a meta-analysis of 18 studies from China, and reported seroprevalence in the general Chinese population and high-risk population to be 0.27% (95% CI 0.02%-0.71%) and 8.3% (95% CI 4.9%-12.5%) (odds ratio 7.2, 95% CI 4.06-13.04) respectively. The prevalence of biopsy-confirmed CeD in high-risk Chinese populations is 4.4% (95% CI 1.5%-8.5%). The seroprevalence is reported to be higher in northern China than that in southern China.<sup>57</sup> These preliminary studies have established the foundation for the exploration of the exact prevalence and regional geographical differences in the prevalence of CeD in China.

While the population-based prevalence of CD remains unexplored in Japan, initial studies have demonstrated that CD is uncommon in Japan. In 2018, Fukunaga et al described only two biopsy-confirmed patients with CD in a study of 2055 subjects including 2008 asymptomatic individuals and 47 adults with chronic abdominal symptoms.<sup>58</sup> The low prevalence is attributable to low frequency of the HLA-DQ2/DQ8 haplotype and a lower dietary consumption of gluten in Japan, although the dietary exposure to gluten has been increasing in Japan.<sup>59,60</sup>

#### 4.5.3 | South East Asia

In a pilot study, including 562 young healthy volunteers from Malaysia, the seroprevalence of CD has been reported to be 1.25% (95% CI 0.78%-1.72%).<sup>61</sup> Similarly, in a study including 1961 Vietnamese children, the seroprevalence, based on anti-tTG Ab, has been found to be 1%, but none of them was positive for EMA.<sup>62</sup>

#### 4.5.4 | Western Asia

CD has been reported from many countries of Western Asia. A systematic review conducted on 22,340 participants from 12 Arabic countries indicated a wide variation in the prevalence of CeD in their general population, highest (3.2%) being in Saudi Arabia and the lowest (0.1%) in Tunisia.<sup>63</sup> Another systematic review and meta-analysis of 63 studies including 36 833 participants from Iran has reported the seroprevalence and prevalence of biopsy-confirmed CD to be 3% (95% CI: 0.03-0.03) and 2% (95% CI: 0.01-0.02) respectively.<sup>64</sup>

#### 4.5.5 | Central Asia and Russia

Savvateeva et al in a review of publications (in both English and Russian language) between 2000 and 2014 and summarised that the prevalence of CD in children has increased in the last few decades and it is at least 0.6%, with significant inter-regional variations. The carrier frequency of HLA-DQ2/DQ8 haplotypes in the Russian population, especially in the western region, seems to be comparable to that in Europe.<sup>65</sup>

Summarising the prevalence studies from Asian Pacific region, a recent systemic review and meta-analysis has shown that the pooled seroprevalence of CD among low-risk groups is 1.2% and that of biopsy-confirmed CD is 0.61% (Table 1).<sup>66</sup> Furthermore, the authors also segregated and reported that the prevalence in the middle east (Iran, Turkey, Saudi Arabia, Israel and Jordan), south-east Asia (India, Malaysia and Egypt) and Eastern Asia. The pooled seroprevalence and prevalence of biopsy-confirmed CD in the Middle East region and South-East region of Asia are 1.6% (95% CI 1.2-2.1) and 0.6% (95% CI 0.4-0.8); and 2.6% (95% CI 0.3-7.2) and 0.8% (0.4-1.4), respectively, which are quite similar to that reported from many European countries. Interestingly, the seroprevalence is found to be lowest (0.06%; 95% CI 0.03-0.09%) in the East-Asian countries.<sup>66</sup>

## 2.5 | Prevalence of CD over time

An increase in the prevalence of CD over time has been well documented in studies including many countries including Italy, Finland and the United States. An analysis of serial serum samples obtained from the same cohort of individuals at two different time points, 15 years apart has indicated that the prevalence has increased five-fold between the years 1974 and 1989 in the United States.<sup>33</sup> In Italy, the prevalence in children increased from 0.88% in 1993-1995 to 1.58% in 2015-2016.<sup>27</sup> Singh et al in a systematic review and meta-analysis also reported an increase in prevalence of biopsy-confirmed CD over time from 0.6% in 1991 to 2000 to 0.8% between 2001 and 2016.<sup>19</sup> (Table 2).

**TABLE 2** Epidemiological characteristics of coeliac disease (CD)<sup>19,24,53,82</sup>

- Both the incidence and prevalence are increasing globally
- Globally 40-60 million people are affected by CD
- A difference between seroprevalence and prevalence of biopsy-confirmed CD has been observed
- CD is more common in children than in adults
- CD is more common in women than in men
- There are differences in the prevalence in different continents
- Even in the same continents, there are differences in the country-specific prevalence and incidence
- The data on the prevalence are not available from many countries, especially Asian and South African countries
- A difference in the population prevalence has been noted the Northern and Southern part of the same country such as India

## 2.6 | Variations in the prevalence of CD as per age, gender and geographical distribution

### 2.6.1 | Children vs adults

While CD was described originally in paediatric patients and believed to be a disease of children only, but it has been realised that it can be diagnosed at any age group including elderly.<sup>19</sup> Such diagnoses do not necessarily indicate late discovery of longstanding CD; they could result from de novo loss of tolerance of gluten in adulthood.

A systematic review including 43 studies has reported the prevalence of biopsy-confirmed CD in the paediatric and adult patients. The pooled prevalence of biopsy-confirmed CD is higher in children in comparison to that in adults (0.9% vs 0.5%). While the prevalence is higher in children, the absolute number of patients with CeD globally and in each country, is likely to be higher in the adult age group because of much higher proportion of adults in any country compared to children in that country.<sup>19</sup> (Table 2).

### 2.7 | Men vs women

As with many other autoimmune diseases, CD is more common in women as compared to men. Several population-based studies from all around the world indicate a significantly higher prevalence among women compared to men.<sup>21,33,37,67</sup>

### 2.8 | Geographical location

A higher prevalence of many autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease has been reported at higher geographical latitudes.<sup>68-70</sup> The associations between the autoimmune diseases and the latitude have been linked to less solar exposure and resultant vitamin D deficiency in them. In a systematic review involving 128 studies, with 155 prevalence estimates representing 40 countries, the prevalence of CD has been

reported to be higher at higher latitudes of 51° to 60° (relative risk of 1.62) and 61° to 70° (relative risk 2.30), in comparison to prevalence at latitudes of 41° to 50° as reference level.<sup>71</sup> In this study, when latitudes were categorised into intervals of 10° latitudinal increments, the prevalence of CD increased incrementally at latitude higher than 40°.

Likewise, the prevalence of CD can vary widely among countries despite geographic proximity. In India, it is more common in Northern part of India compared with that in the Southern part of India.<sup>53</sup> Similarly, a difference in prevalence has been observed in two adjacent countries such as a prevalence of 1.4% in Finland compared with only 0.6% of people in the adjacent Russian Karelia despite of no significant differences in compatible HLA haplotypes.<sup>72</sup>

## 2.9 | Racial and ethnic differences in the prevalence of CD

There are many studies which suggest that there are racial and ethnic differences in the prevalence of CD.<sup>73</sup> In a racially and ethnically stratified national study, CD seroprevalence was highest in the non-Hispanic whites (1.08%) and it was much lower in Mexican-Americans (0.23%), other Hispanics (0.38%) and non-Hispanic blacks (0.22%).<sup>73</sup> Similarly, in an analysis of duodenal biopsies from 454,885 patients from a nationwide pathology database, Krigel reported that among subjects undergoing duodenal biopsy, the prevalence of CD was significantly lower in South Indian, East Asian and Hispanic when compared to other Americans. Also, the prevalence among Middle-Eastern and Jewish patients was not significantly different when compared with other Americans. Finally, in this database, North Indian patients identified with ancestry in the Punjab region had a significantly higher prevalence of CD on duodenal biopsy compared to all other North Indian patients.<sup>74</sup> Interestingly, the finding of low CD prevalence among Hispanics and Mexican-Americans is in contrast with high prevalence reported in other countries such as Mexico, Argentina and Brazil. Ethnic differences in the seroprevalence have been reported from several other countries.<sup>75,76</sup> In a cross-sectional study of over 4000 Dutch children, western ethnicity was associated with 6.9-fold higher odds of coeliac autoimmunity compared to those with non-western ethnicity.<sup>76</sup> Similarly, in a database study from Israel, CD was significantly lower in people of African, Asian and former Soviet Union origin.<sup>75</sup>

## 3 | INCIDENCE OF CD

The incidence of CD is generally expressed as a rate, that is, the number of new diagnosed patients with CD per 100 000 subjects over 1 year in a defined population. While there are multiple reports on the incidence of CD from Europe, North America and Oceania, population-based studies on incidence are lacking from Africa, Asia and Latin America.

With better awareness about the clinical polymorphism of CD and increasing use of serological tests in the clinical practice, the

incidence of CD has greatly increased in many western countries during the last decades.<sup>77,78</sup> For instance, 20 times more patients were diagnosed in the United Kingdom during 2010-2014, than that during 1975-1979.<sup>79</sup> In the United States (Olmsted County, Minnesota), the overall age- and sex-adjusted incidence has increased from 11.1 per 100 000 persons/year in 2000-2001 to 17.3 in 2008-2010.<sup>79</sup>

In a nationwide population-based cohort study 1990-2015 based on duodenal biopsy showing villous atrophy, the mean age-standardised incidence rate during the study period has been found to be 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 CD is estimated to be 1.8% (2.3% in females and 1.4% in males).<sup>80</sup>

Not only in the Europe and North America, temporal trends show a steady increase in CD autoimmunity incidence between the years 2007-2015. Thus, the incidence of CeD autoimmunity increased from 25.4 per 100 000 in 2007 to 52.3 per 100 000 person-years in 2015 (Incidence rate ratio of 2.06, 95% CI 1.81-2.26).<sup>81</sup> Overall, there is paucity of population-based studies reporting of incidence of CD from many parts of the world except for the a few countries.

In a recent systematic review and meta-analysis, King et al. reported the differences in incidence of CD before and that after the year 2000. The pooled average annual incidence has been estimated to be rising by 7.5% (95% CI: 5.8-9.3) per year over the past several decades.<sup>82</sup> The systematic review showed that the pooled incidence of CD in women and men is 17.4 (95% CI: 13.7-21.1) and 7.8 (95% CI: 6.3-9.2) per 100 000 person-years respectively. Children specific incidence of CD is higher (21.3 per 100 000 person-years) in comparison to that of the adults (12.9 per 100 000 person-years).<sup>82</sup> (Table 1).

In another systematic review and meta-analysis of incidence of CD in children in Europe showed a large increase in the incidence across Europe and it has reached 50 per 100 000 person-years in Scandinavia, Finland and Spain.<sup>24</sup> The median age at diagnosis of CD has increased from 1.9 years before 1990 to 7.6 years since 2000.<sup>24</sup>

As discussed above, while the incidence rates for CD are increasing in many countries such as the United Kingdom,<sup>79</sup> the United States<sup>83</sup> and New Zealand,<sup>84</sup> the incidence rate in Finland and Sweden has reached the peak and it is stabilising.<sup>85,86</sup> This increase in incidence is not likely only due to improvement in the rate of diagnosis and increase in the awareness of the disease among physicians but also due to changes in our environment and eating practices.<sup>33,87</sup> (discussed below).

The epidemiological characteristics of CD are summarised in Table 3.

## 4 | MALIGNANCY IN PATIENTS WITH CD

A Swedish population-based cohort of individuals hospitalised with CD or dermatitis herpetiformis showed an increased risk of malignancy, especially lymphomas (standardised incidence ratio 6).<sup>88</sup>



TABLE 3 Risk factors for coeliac disease

Essential factors	Risk factor modifiers
Gluten	Amount of gluten ingestion Timing of gluten introduction during weaning Gluten processing by gut microbiota
Genetic MHC gene: HLA-DQ2, HLA-DQ8	Non-HLA genes Epigenetic factors Breastfeeding Childhood infection Use of antibiotics in childhood Gut microbiota Socioeconomic status Caesarean section

The risk, however, decreased on follow-up. Another study from Sweden showed that most of the risk of gastrointestinal cancers in patients with CeD is within 1 year of the diagnosis.<sup>89</sup> Additionally, patients with type 2 refractory CD are at higher risk of developing enteropathy-associated T-cell lymphoma (EATL) (~50% after 5 years of RCD 2 diagnosis).<sup>90,91</sup>

## 5 | MORTALITY ASSOCIATED WITH CD

Several large population-based studies have reported a 1.2- to 2- fold increase in mortality risk with CD. In a recent retrospective, population-based cohort study of 49 829 patients with CD diagnosed during 1969-2017, overall mortality was still found to be increased in patients compared with controls (hazard ratio of 1.21, 95% CI 1.17, 1.25).<sup>92</sup> In this study, the increased mortality risk was still present in patients diagnosed during the years 2010-2017 suggesting that despite improved awareness, active case finding, and widespread availability of GFD, patients with CD continue to have a small but significant increase in mortality risk compared with general population. The increased mortality risk in patients with CD appears to be diminished in the years after diagnosis suggesting the beneficial effect of GFD on mortality.<sup>92,93</sup> Although some studies have shown that the long-term mortality risk is restricted to only those diagnosed in childhood,<sup>93</sup> others have found that the mortality risk is increased across all age groups.<sup>92</sup> The increased mortality in CD appears to be in part due to the increased risk of non-Hodgkin's lymphoma. However, increased mortality risk due to cardiovascular as well as respiratory causes has also been observed.<sup>92</sup> The exact aetiology of this increased respiratory and cardiovascular related mortality is not clear, but chronic inflammation and increased susceptibility to pneumococcal infections might play a role.<sup>92</sup>

## 6 | RISK FACTORS FOR CD

CD occurs because of interaction between genetic (HLA and non-HLA genes) and environmental factors.<sup>94</sup> While exposure to gluten

in a genetically predisposed individual is essential for occurrence of CD, there are, however, other risk factors such as non-HLA related genes and epigenetic factors, infant feeding (amount of gluten, age of introduction of gluten, breastfeeding), mode of delivery, childhood infections, antibiotic exposure and gut microbiota that do play a role in the pathophysiology of CD. (Table 3). The data from the Swedish twin registry (107 000 twins out of whom 513 had CD) predict that HLA and non-HLA genetics explain 68% of the risk of CD and environmental factors explain 32% of the risk, assuming that everyone in the population consumes gluten.<sup>95</sup>

### 6.1 | Wheat, barley and rye

In the evolutionary process, the genome of wheat has changed from diploid (14 chromosomes) to hexaploid genome (42 chromosomes).<sup>96</sup> The genome of the most ancient wheat is diploid and it is named as AA, BB and DD. These grass-like wheat species had a very low seed yield and their seed dropped easily. Natural hybridisation between two of these diploid species led to birth of the tetraploid, *Triticum* species, having AABB genome. Finally, around 4000 BC, natural hybridisation between *T. turgidum* (dicoccum) carrying the AABB genome and a wild diploid species *Aegilops tauschii* carrying the D genome led to origin of bread wheat (*Triticum aestivum*). The introduction of the D genome in the wheat improved the bread-making properties of the wheat.<sup>97,98</sup>

The protein content of wheat grains varies between 8% and 17% of its total mass. Gluten comprises of 78%-85% of the total wheat endosperm protein. Gluten proteins can be divided into two main fractions according to their solubility in aqueous alcohols: the soluble gliadins and the insoluble glutenins. Gliadins are mainly monomeric proteins with molecular weights (MWs) around 28 000-55 000 and they are classified according to their different primary structures into alpha, beta, gamma and omega type. Glutenin consists of glutenin subunits of high (MW 67 000-88 000) or low MW (MW 32 000-35 000), that are connected by intermolecular SS bonds. The aggregation between gliadins and glutenins is facilitated by the non-covalent bonds such as hydrogen bonds, ionic bonds and hydrophobic bonds and they provide the structural and physical properties of the wheat flour dough. Glutenins confer elasticity, while gliadins mainly confer viscous flow and extensibility to the gluten complex. Thus, gluten is responsible for most of the viscoelastic properties of wheat flour dough, and it is the main factor dictating the use of wheat in the making of bread and pasta.<sup>99</sup>

Gliadins and glutenins have a unique amino acid composition with a high content of proline (15%) and glutamine (35%). Moreover, they contain domains with numerous repetitive sequences rich in these amino acids. The incomplete digestion of gliadins by the digestive tract enzymes leads to the generation of peptides, many of which are immunogenic for patients with CD.<sup>3,99</sup>

Over the past five decades, several changes in the pattern of wheat consumption have been observed including an increase in per capita consumption of wheat, an increase in the use of gluten in food processing and an increase in the consumption of processed foods. Furthermore,

an increase in CD-related T-cell stimulatory epitopes has also been observed in wheat. It is conceivable that these changes in the wheat consumption pattern and increase in T-cell stimulatory epitopes in wheat may be the reasons for an increase in the incidence of CD world over.<sup>100</sup>

## 6.2 | Genetic risk factors

CD is considered to be a polygenic disease with a complex non-Mendelian pattern of inheritance, involving both MHC and non-MHC genes. The strong genetic predisposition for CD is demonstrated by concordance rate of 80% in monozygotic twins and 20% in dizygotic twins.<sup>101,102</sup> Furthermore, the prevalence of CD in the first-degree relatives of patients with CD has been reported to vary from 1.6 to 38%.<sup>103-105</sup> A systematic review and meta-analysis have shown that 7.5% of first-degree relatives and 2.3% of second degree relatives have CD.<sup>88</sup> The risk of CD is 1 in 7 in sisters, 1 in 8 in daughters, 1 in 13 in sons, 1 in 16 in brothers, 1 in 32 in mothers and 1 in 33 in fathers.<sup>106</sup>

### 6.2.1 | HLA genes

The most dominant genetic risk factors that predispose to CD are the genotypes encoding the HLA class II molecules, HLA-DQ2 (encoded by HLA-DQA1\*0501 and HLA-DQB1\*02) and HLA-DQ8 (encoded by HLA-DQA1\*0301 and HLA-DQB1\*0302).<sup>107,108</sup> About 90%-95% of individuals with CeD carry the DQ2 heterodimer encoded either in cis or in trans, and/or DQ8.<sup>109</sup> Deamidated gliadin peptides have a high binding affinity to HLA-DQ2 and HLA-DQ8 molecules, which explains the immunogenicity of gluten in carriers of HLA-DQ2 and HLA-DQ8.<sup>110</sup>

The HLA-DQ2 heterodimer is frequently found in white populations in western Europe, North America (20-30%), northern and western Africa, middle east Asia, Northern India and central Asia, whereas HLA-DQ8 is more prevalent in Latin America and Southern part of India. One of the highest prevalence of CD has been observed in Saharawi population of Arab-Berber origin and this has been attributed to higher frequencies of HLA-DQ2 in them.<sup>111</sup>

More importantly, most of those people having these alleles will never develop CD. In a large prospective observational study involving 6403 infants with HLA-DQ2/-DQ8 haplotype, 12% and 5%, of the children at a median follow-up of 5 years, developed coeliac autoimmunity (serology positive) and CD (mucosal biopsies showing villous atrophy or anti-tissue tTG Ab 10 times over the cut-off value) respectively.<sup>112</sup> In the follow-up study of the same group of children after a median follow-up of 9 years, 18% and 7% of them developed coeliac autoimmunity and CD, respectively. Furthermore, a person with HLA-DQ2 homozygosity is at five times higher risk of developing CD than someone with a single HLA-DQ2 and a correlation has been found between homozygosity for the genes encoding HLA-DQ2 molecule and the development of serious complication such as refractory CD and EATL, which implies a gene-dose effect.<sup>113,114</sup>

### 6.2.2 | Non-HLA genes

While HLA molecules play very significant role in the pathogenesis of CD, only HLA related factors are not sufficient to explain the occurrence of the disease in ~3% of all individuals harbouring HLA-DQ2 or DQ8 haplotype.<sup>115</sup> Sequencing of the human genome opened the possibility of mapping genetic variants and analysing their association with complex diseases. Many additional genetic loci, outside the HLA region, have been found to be associated with CD,<sup>116-118</sup> the relative risk of each of these other non-HLA genes is small. These non-HLA variants are mainly single nucleotide polymorphism (SNP) and they are located both in the coding and non-coding regions of the DNA. The SNPs in the encoding region such as MMEL1, SH2B3, IRAK1 and NCF2CeD play important roles in adaptive immune response, immune cell signalling, T-cell maturation and cell differentiation.<sup>117</sup> In addition, genes related to mucosal integrity (*PARD3* and *MAGI2*), epithelial function, and even metabolism are also associated with CD risk. GWAS has also identified risk variants in the region harbouring the *IL2* and *IL21* genes. *IL-2* is involved in T-cell activation and proliferation while *IL-21* enhances B-cell, T-cell and NK-cell proliferation.<sup>115</sup>

Interestingly, the presence of both HLA and non-HLA alleles has been found to favour the occurrence of CD. The risk of developing CD increased sixfold in the presence of 13 non-HLA alleles along with typical HLA genes, compared to those with zero to five alleles.<sup>119</sup>

### 6.2.3 | Epigenetic factors

Currently, emerging evidences suggest a high impact of non-protein-coding genes on the gene expression and disease risk.<sup>120</sup> These epigenetic variations may be playing a role in the pathogenesis of CD. MicroRNAs (miRNAs) are short non-coding RNAs that regulate gene expression at the post-transcriptional level and play a key role in the pathogenesis of autoimmune and gastrointestinal diseases. There is evidence to suggest that many miRNAs are dysregulated in intestinal biopsies of patients affected by CD. miRNAs such as miR-31-5p, miR-192, miR-194, miR-449a and miR-638 have been reported to be dysregulated in patients with CD and may affect many important cellular functions such as Wnt signalling, cell proliferation and differentiation, and adherent junction pathways.<sup>121</sup> These epigenetic variations in patients with CD can explain individual variability in the phenotype of CD and in depth studies are required to further explore this area.

## 6.3 | Other environmental risk factors which might influence the incidence of CD

A steady rise in the incidence of autoimmune disorders as well as allergic disorders concomitant with a decrease in the incidence of infective illnesses, as observed during the past few decades, have



been attributed to the hygiene hypothesis.<sup>122,123</sup> Chronic infections acquired during childhood induce immune tolerance to various extrinsic antigens by stimulating regulatory immune cells. Helminthic infections have been shown to regulate and modulate the immune system of the host in such a way to suppress Th1-induced immune response in the hosts. Therefore, eradication of helminthic infection in a cleaner environment leads to a release of helminthic infection-induced suppression of Th1 immune response and thus a surge in Th1-induced diseases.<sup>124</sup>

There are factors other than hygiene hypothesis that also may predispose an individual to develop CD. Some of these factors include age at the introduction of wheat during weaning, amount of gluten ingestion in the early part of life, breastfeeding and infections during the early childhood. (Table 3).

### 6.3.1 | Age at the introduction of gluten

The timing of exposure to gluten in infancy has been proposed to be a risk modifier of development of CD. Introduction of solid food to infants before certain degree of maturation of the intestinal immune system may lead to development of intolerance to food proteins. As for infants at risk of developing food allergies, there are evidences that suggest that introducing solid foods before 3 month of life is detrimental and it should be avoided. Therefore, infant feeding practices, particularly regarding the introduction of gluten, have been the focus of primary prevention strategies.

The Swedish epidemic of CD (1984-1996) arose as a consequence of change in the infant feeding formula.<sup>125</sup> From 1985 to 1987, the annual incidence rate in children below 2 years of age increased fourfold to 200-240 cases per 100 000 person-years, and by 1995, a sharp decline to the previous level of 50-60 cases per 100 000 person-years was observed in Sweden. The prevalence of CD was almost fourfold higher in this birth cohort compared with that in infants born after the epidemic, in which commercial feeding formula was introduced gradually while continuing breastfeeding.<sup>125</sup> It was later observed that during that time the manufacturers of commercial infant food had increased the gluten content of commercial infant food and hence the infants were exposed to high quantity of gluten inadvertently. This assumption is also supported by a recent 10-year observational study in which the investigators explored the right age for the introduction of solid food in the development of CD. The investigators introduced gluten-containing cereals before 3 months of age, between 3 and 7 months and at 7 months or later in a cohort of 1560 children at risk of CD or type I diabetes for development of CD autoimmunity or CD. Of 51 children who developed CD autoimmunity in the cohort, those exposed to gluten in the first 3 months of age had a fivefold higher risk of CD autoimmunity compared to those exposed at 4-6 months (hazard ratio, 5.17; 95% CI; 1.44-18.57); and those who received gluten for the first time at 7 months of age or after showed a slightly increased hazard ratio compared

with those exposed at 4-6 months (hazard ratio 1.87; 95% CI 0.97-3.60).<sup>126</sup> Along with the experience of Swedish epidemic, the results of this study suggested an existence of a "window period," during which solid food or gluten should be introduced in order to minimise the risk of subsequent development of CD.

A recent growing body of evidence, however, challenges the notion that solid food (including gluten-containing foods) should be introduced beyond the sixth month of life.<sup>127,128</sup>

For the primary prevention of CD, the age of first introduction of gluten in infants was further explored in randomised trials.<sup>25,129,130</sup>

In a multinational, multicentre randomised trial, 944 infants were randomly assigned to groups given low-dose daily gluten or placebo at age 4 months, followed by full introduction of gluten at age 6 months in both groups. The prevalence of CD was 12.1% at 5 years, with no significant difference between groups.<sup>130</sup> In another multicentre trial conducted throughout Italy, 533 infants were randomly assigned to groups that were introduced to gluten at age 12 months or at age 6 months. By the age 10 years, 16.8% developed CD, with no significant difference between groups in disease development, apart from a slightly delayed risk in the 12-month group.<sup>129</sup> The results of these randomised trials overturned longstanding beliefs, based on observational studies, that the timing of gluten exposure affected the risk of development of CD. A systematic review and meta-analysis by the PREVENTCD group also showed a similar rates of CD in high-risk children irrespective of introduction of gluten at age of 4, 6 or 12 months.<sup>128</sup> These results led to liberalisation of feeding recommendations by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition, which issued guidelines that advised introducing gluten any time between 4 and 12 months.<sup>131</sup>

### 6.3.2 | Amount of gluten ingestion in early part of life

Furthermore, rather than timing of introduction of gluten at the time of weaning, three studies recently have shown that ingestion of a larger quantity of gluten at weaning is associated with a higher risk of developing CD in future.<sup>112,132,133</sup> In a cohort study by the TEDDY (The Environmental Determinants of Diabetes in the Young) study group, Aronsson, et al reported an association between gluten intake during the first 5 years of life with the incidence of CeD autoimmunity and CeD in 6605 at high-risk children.<sup>112</sup> Overall, ingestion of higher quantity of gluten during the first 5 years after birth was associated with an higher risk of CD autoimmunity and CD. The post-hoc analysis, that focused on dietary gluten intake at the age of 2 years, revealed that the daily gluten consumption of as little as 2 g (equivalent to one slice of bread) is associated with an higher risk of development of CD autoimmunity or CD.<sup>112</sup> The risk further increased with each gram of gluten. Two other cohort studies also confirmed that children consuming higher amount of gluten have a higher risk of developing CD.<sup>132,133</sup>

### 6.3.3 | Breastfeeding

The protective effect of breastfeeding on the development of food allergic disorders has been proposed for a long time.<sup>134,135</sup> While several studies have described protective effect of breastfeeding on the development of CD,<sup>136-138</sup> others have not confirmed such an association.<sup>126,129,130,139,140</sup> Studies as early as in 1950s have shown a delay in the onset of diarrhoea by increasing the duration of breastfeeding in patients of CD. Moreover, a significant correlation has been reported between the duration of breastfeeding and the age at the diagnosis of CD suggesting that breastfeeding delays the onset of CD.<sup>126</sup> Furthermore focussing on two other factors namely duration of the breastfeeding and the introduction of gluten at the time of breastfeeding, various studies have provided contradicting results. A systematic review, by PREVENTCD group in 2015, has shown that there is neither a relationship between breastfeeding and the future development of CD, nor between duration of breastfeeding and the appearance of the disease.<sup>128</sup>

### 6.3.4 | Childhood infections, gut microbiota and antibiotics

#### 3.4.1 | Childhood infections

Episodes of gastroenteric infection during infancy such as those with reovirus or rotavirus have been proposed to be the predisposing factors for future development of CD.<sup>141</sup> It is known that colonisation of intestinal microbiota in the early part of life is essential not only for normal physical growth and development but also for maturation of the immune system.<sup>142,143</sup> Several mechanisms including immunomodulation and disruption of the mucosal barrier have been proposed to explain an association of CD with childhood infection.<sup>144-153</sup> In an Italian study, gastrointestinal infections requiring hospitalisation and antibiotic usage during first year of the life have been found to be associated with CD (incidence rate ratio of 2.04[1.30-3.22], 1.24[1.07-1.43]).<sup>154</sup> TEDDY group of investigators has recently reported that the childhood gastrointestinal infection, not respiratory infections, is associated with increased risk of coeliac autoimmunity in genetically susceptible individuals (hazard ratio 1.33).<sup>155</sup> Furthermore, a systemic review and meta-analysis including 19 observational studies has shown that any infection in childhood is associated with a 37% increase in the odds of developing CD, particularly among those requiring hospitalisation.<sup>156</sup>

#### 3.4.2 | Gut microbiome

Not everyone with risk factors such as ingestion of gluten and genetic susceptibility develop CD. Modification of immunogenic peptides by secretion of gluten-degrading enzymes by the intestinal microbiota has been proposed to be one of the factors for the risk. Human gastrointestinal tract has bacteria secreting proteolytic enzymes that degrades gluten or degrade immunogenic peptides such as mer-33 peptide, suggesting a protective role of gut microbiome.<sup>157</sup> Exclusively breastfed and vaginally delivered infants, at high

risk of developing CD (family history of CD and HLA-DQ2/-DQ8 positive), have higher proportions of Firmicutes and Proteobacteria and lower proportions of Actinobacteria in their gut compared with those infants at low risk (HLA-DQ2/DQ8 negative).<sup>158</sup> *Pseudomonas* obtained from patients with CD produces elastase enzyme that degrades gluten into immunogenic peptides. Hence, not only might gut microbiota protect individuals from developing CD, but the peptides secreted by specific intestinal bacteria also synergises with gluten to induce more severe inflammation.<sup>159,160</sup>

A study "Coeliac Disease Genomic, Environmental, Microbiome, and Metabolomic Study" (CDGEMM) is being conducted in the United States, Italy and Spain and likely to throw more light on the role of gut microbiota in patients with CD.<sup>161</sup>

#### 3.4.3 | Antibiotic exposure

Additionally, exposure to antibiotics during early life can modulate the gut microbiota and antibiotic exposure has been associated with an increased risk of CD. In a systemic review and meta-analysis including six observational studies on exposure to antibiotics was also associated with 20% increase in the risk of CD (odds ratio, 1.2; 95% CI: 1.04-1.39;  $P < 0.001$ ).<sup>156</sup>

#### 3.4.4 | Socioeconomic factors

An epidemiological survey including school children, having similar genetic susceptibility and gluten intake, living in a prosperous area of Finland and in an adjacent unprivileged region of Russia, has suggested that worse socioeconomic conditions might protect against the development of CD.<sup>72</sup> Several European studies also have shown that children living in more socioeconomic deprived areas are less likely to be diagnosed with CD.<sup>162-164</sup> High maternal education has also been linked to an increased risk of CD in the offspring.<sup>154</sup> On the contrary, no substantial association has been observed between the socioeconomic status and the occurrence of CD.<sup>164</sup>

Similarly, in a US study from tertiary care centre, black race and public insurance were both individually associated with 90 % decreased odds of having appropriate work-up for CD among patients presenting with iron deficiency anaemia and/or chronic diarrhoea.<sup>165</sup> Furthermore, coeliac patients with lower income also had worse CD-related health and greater symptoms. In another study including over 300 patients, those with low income had six times odds of greater symptoms compared with those with high income.<sup>166</sup>

There are more questions than answers on the environmental risk factors for CD. Hopefully, many ongoing cohort studies including TEDDY, PREVENT CD and "Coeliac Disease Genomic, Environmental, Microbiome, and Metabolomic Study" (CDGEMM) will throw more light on environmental risk factors, some of which may be explored for the primary prevention of CeD.<sup>161,167</sup>

## 7 | CONCLUSIONS

While CD is now a global disease and affects approximately 40- 60 million people worldwide, there still are regions, such as many Asian

countries, from where population-based prevalence estimates are not available. Despite an increase in the awareness about its high prevalence of CD and wide clinical presentations, majority of patients with CD still remains undiagnosed, misdiagnosed or experience a significant delay in the diagnosis. There is not only a need to detect undiagnosed patients by increasing the awareness about CD among the general population and healthcare professionals, but also the establishment of infrastructure including diagnostic facilities and gluten-free food supply chain.

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## DATA AVAILABILITY STATEMENT

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