

Celiac Disease in Asia beyond the Middle East and Indian subcontinent: Epidemiological burden and diagnostic barriers

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Abstract

Celiac Disease (CD) had been considered uncommon in Asia for a long time. However, several studies suggested that, in the Indian subcontinent and Middle East countries, CD is present and as prevalent as in Western countries. Outside these Asian regions, the information about the epidemiology of CD is still lacking or largely incomplete for different and variable reasons. Here, we discuss the epidemiological aspects and the diagnostic barriers in several Asian regions including China, Japan, Southeast Asia and Russia/Central Asia. In some of those regions, especially Russia and Central Asia, the prevalence of CD is very likely to be underestimated. Several factors may, to a different extent, contribute to CD underdiagnosis (and, thus, underestimation of its epidemiological burden), including the poor disease awareness among physicians and/or patients, limited access to diagnostic resources, inappropriate use or interpretation of the serological tests, absence of standardized diagnostic and endoscopic protocols, and insufficient expertise in histopathological interpretation.

Key Words: Celiac disease; Epidemiology; Prevalence; Asia; China; Japan; Russia; Central Asia; HLA-DQB1; Diagnostic barriers

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Core Tip: This editorial discusses the main epidemiological characteristics of Celiac Disease in Asia outside the Indian subcontinent and Middle East countries. Indeed, information about the epidemiology of Celiac Disease is still lacking or largely incomplete in those Asian regions (China, Japan, South-East Asia, and Russia/Centra

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Asia), where the disease prevalence is likely be underestimated. Factors contributing to diagnostic difficulties in these Asian regions are discussed.

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INTRODUCTION

The global prevalence of Celiac Disease (CD) is estimated to be around 1% in the general population. However, this estimation is based on epidemiological studies that mainly come from the European and South/North American continents[1,2]. CD had been considered to be uncommon in Asia for a long time, but several studies published in the previous two decades demonstrated that CD is present and is as prevalent in the Indian subcontinent and in the Middle East, as it is in Western countries[3-5].

A few years ago, a meta-analysis by Singh *et al*[6] reported that the pooled prevalence of CD in Asia was around 0.5% without any significant difference between children and adults. Except for one study from Malaysia, all the clinical studies were from the Middle East (Turkey, $n = 5$; Iran, $n = 4$; Israel, $n = 2$; Saudi Arabia, $n = 2$; Jordan, $n = 1$) and India ($n = 3$). A recent study estimated that the prevalence of CD might be as high as 1% even in those Asian countries, based on an assessment of the HLA-DQB1*02 allelic frequencies and wheat consumption in the general population[7]. Indeed, the HLA-DQB1*02 allelic variant is the major HLA-related CD predisposing allele, and the appropriate HLA genetic background is as necessary (but not sufficient) as the dietary gluten intake to trigger of the immunopathological process underlying CD[8,9]. In India, this estimate was confirmed by a community-based study by Makharia *et al*[10], who found a CD prevalence of 1.04% in the north of India, where both the dietary habits and HLA-DQ genetic background favor the development of CD. A study from Iran including 1,500 healthy school children serologically screened for CD, led to a biopsy-confirmed diagnosis of CD in 0.6% of this pediatric cohort. As most of the cases appeared to be silent, it is reasonable to expect a higher prevalence in the general population[11]. The situation may be the same in Turkey, where Tatar *et al*[12] screened 2,000 healthy blood donors for CD markers and found that 1.3% ($n = 26$) were positive, and 12 donors (0.6%) were diagnosed with CD after biopsy. Considering that most of the serologically positive donors ($n = 14$) could not be contacted or refused endoscopy and all the diagnosed cases had been silent, the overall CD prevalence is probably greater.

For various reasons, epidemiological information about CD in other Asian regions is incomplete. The available data from China, Japan, Southeast Asia, and Russia/Central Asia are discussed below.

CHINA

In the last decade, more studies investigating the epidemiology of CD have been published from China than from the other Asian regions discussed here. In 2011, Wang *et al*[13] published a national multicenter study describing 14 Chinese children histologically diagnosed with CD after serological screening because of chronic diarrhea. Yuan *et al*[14] reported that the presence of DQB1*0201 allele was not negligible in the Chinese population, with an overall frequency of 10.5%. The highest frequency of HLA-DQB1*02 was > 20%-25% in the northwestern region, where non-Chinese ethnic minorities (*e.g.*, Kazakh and Uyghur ethnicities) are present in the population. Recently, the same authors reported a CD seropositivity rate of 2.19% in a cross-sectional study including 19,778 Chinese adolescents and young adults[15].

Dietary exposure to gluten has increased over the past 50 years in the Chinese population. Wheat has become the second most consumed staple food, after rice. China is one of the world's largest producers and consumers of wheat, especially in

the northern regions. Therefore, CD is an emerging disease in this country; and, despite the lack of epidemiological studies with a complete diagnostic definition, the awareness of this disease and its potential impact on health should be increased in such a large population[14]. In 2019, Chen and Li[16] reported that lack of awareness among the population and health professionals have contributed to the hidden epidemiological burden of CD in China. They also reported that local lack of resources could limit the access to standardized tissue acquisition and histological evaluation. Consequently, in most studies, seropositive individuals could not undergo the duodenal biopsy needed for the confirmation of a CD diagnosis.

JAPAN

In Japan, the epidemiological burden of CD is extremely low. In 2018, Fukunaga *et al*[17] described only two biopsy-based CD diagnoses in a group of 2,055 people including 2,008 asymptomatic individuals and 47 adults complaining of chronic abdominal symptoms, which corresponds to < 0.1% prevalence. That finding is consistent with the very low frequency of the HLA-DQ2/DQ8 immunotype. Indeed, in a study including 371 unrelated healthy apheresis blood donors, the HLA-DQB1*02 allele frequency was reported to be < 1% even though the DQB1*03:02 allele is relatively common (10.8%)[18]. Although the dietary exposure to gluten has been increasing in Japan, the consumption of wheat is still relatively low (it is estimated to be approximately one-third of that consumed in Western countries)[17].

The same research group reported a CD seropositivity rate (based on anti-tissue transglutaminase (tTG) immunoglobulin (Ig) A antibody) of 0.19% in 2,005 Japanese adults tested in 2008-2013. That result is consistent with another study that reported a positivity rate of 0.2% (based on a 10 U/mL titer cutoff) in 2014-2016[17,19]. Because of the presumed low prevalence, in Japanese clinical practice, CD may be rarely considered by physicians who manage patients with chronic abdominal symptoms[17].

It must be emphasized that the available studies were mostly, if not completely, focused on asymptomatic/healthy people. The actual prevalence of CD seropositivity and diagnosis may thus be higher than that reported so far. Nevertheless, Hokari and Higashiyama[20] observed that Japanese physicians are unlikely to overlook CD, as the endoscopic assessment is well-established in Japan for patients complaining of chronic abdominal symptoms. This procedure is performed by well-trained endoscopists and the histopathological appearance of CD mucosa is well-known. Therefore, the low epidemiological burden of CD in Japan is considered to be real: it is consistent with the immunogenetic background and dietary habits, and there are no major diagnostic barriers. However, this situation may change in the near future if wheat consumption increases.

SOUTHEAST ASIA

Few clinical studies assessed the epidemiological burden of CD in this Asian region[21]. In most countries of Southeast Asia, the allele frequency of HLA-DQB1*02 is estimated to be < 10%-15%[6]. The low dietary intake of gluten also contributes to the low prevalence of CD. In Vietnam, CD autoimmunity was assessed in 1,961 children and around 1% were found positive for anti-tTG IgA[22]. In Thailand, CD serology was assessed in 46 children with type 1 diabetes mellitus and only one child was positive for anti-tTG IgA. Considering an expected prevalence of > 5% (and up to 10%) in such a risk group, the prevalence of CD is assumed to be low in Thai children and in the general population[23,24].

In Malaysia, Yap *et al*[25] reported a relatively high CD seroprevalence of 1.25% in healthy young adults. This finding might be explained by the fact that the Malaysian population includes three main ethnicities (*i.e.* Malay, Chinese, and Indian), but HLA genotyping was not performed in that study. These authors noted that CD is underdiagnosed in Malaysia and discussed the diagnostic barriers in this country. Lack of medical awareness of CD (resulting in a low rate of request for CD serology tests), the use of less sensitive CD serological markers, inappropriate application of endoscopic protocols, and under-recognition of mild CD histopathological patterns, were all considered to be contributing factors.

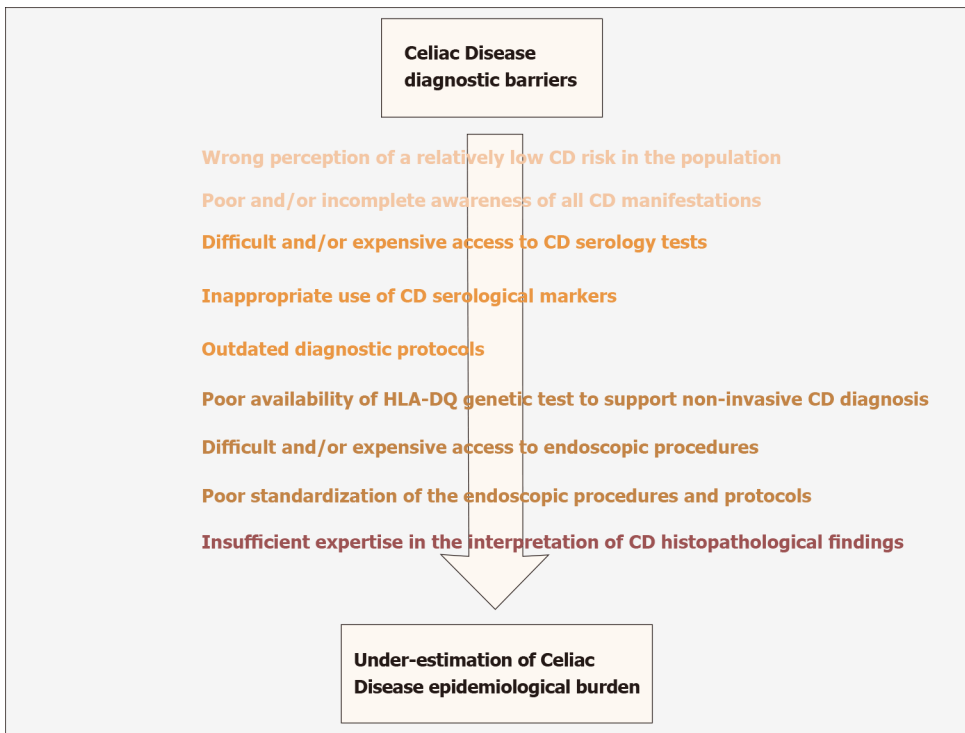


Figure 1 Schematic overview of CD diagnostic barriers in Kazakhstan (CD: Celiac Disease).

RUSSIA AND CENTRAL ASIA

A review by Savvateeva *et al*[26] is the primary English-language publication of the overall and indirect epidemiological evidence of CD in Russia. Most studies considered in this review were conducted from 2000 to 2014 and were published in Russian language. The authors concluded that the prevalence of CD in children has increased in the last few decades and is at least 0.6%, although significant inter-regional variations should be considered, because of the geographical extent of this region. 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. Savvateeva *et al*[26] reported epidemiological trends and prevalence rates similar to those in Europe, but do not discuss potential barriers hampering CD diagnosis in their country. However, they do declare well-established therapeutical support and follow-up protocols for CD patients in Russia.

Epidemiological data from Central Asia and, more precisely, from Kazakhstan are also mentioned in the aforementioned article by Savvateeva *et al*[26]. They reported a CD prevalence of < 0.4% or one case in every 262 children. However, the diagnostic approach based on anti-gliadin antibodies and the study design were prone to a significant underestimation of the actual prevalence[21,26]. Moreover, our group recently showed that the carrier frequencies of HLA-DQB1*02 and HLA-DQB1*03:02 in Kazakhstani healthy blood donors are 38% and 12.5%, respectively, and these numbers are comparable to those described in Caucasian populations. Considering the high consumption of wheat foods in Kazakhstan, we concluded that it is reasonable to expect that the CD prevalence in this country may be comparable to that reported in Europe[27].

Large well-designed clinical studies are needed to provide a reliable estimate of the CD epidemiological burden in Central Asia. It is likely that CD is underdiagnosed in Kazakhstan. Several barriers currently contribute to the underdiagnosis of CD in this country, including the inappropriate use of serological tests, limited access to diagnostic tools for economic reasons, the absence of standard protocols for endoscopic procedures, and difficulties in histopathological interpretation[27,28]. The combined effects of all those obstacles lead to the underestimation of the diagnostic and epidemiological burden in this country, as summarized in Figure 1. These considerations might also apply in other regions of Central Asia that have even fewer economic resources.

CONCLUSION

Outside the Indian subcontinent and Middle East countries, the epidemiological burden of CD in Asia is very likely to be underestimated, especially in Russia and Central Asia, where wheat is a staple food and the genetic predisposition to CD is comparable to Europe.

In agreement with other authors[29,30], several factors (that vary by country and regions) can contribute to hamper CD diagnosis and, thus, the estimation of its epidemiological burden. Overall, these factors include poor disease awareness among physicians and/or patients, limited access to diagnostic resources (because of economic and/or organizational and/or geographical reasons), inappropriate use or interpretation of the available serological tests, absence of standardized diagnostic and endoscopic protocols, and insufficient expertise in histopathological interpretation.

REFERENCES

- 1 **Lindfors K**, Ciacci C, Kurppa K, Lundin KEA, Makharia GK, Mearin ML, Murray JA, Verdu EF, Kaukinen K. Coeliac disease. *Nat Rev Dis Primers* 2019; **5**: 3 [PMID: 30631077 DOI: 10.1038/s41572-018-0054-z]
- 2 **Lebwohl B**, Sanders DS, Green PHR. Coeliac disease. *Lancet* 2018; **391**: 70-81 [PMID: 28760445 DOI: 10.1016/S0140-6736(17)31796-8]
- 3 **Ashtari S**, Pourhoseingholi MA, Rostami K, Aghdaei HA, Rostami-Nejad M, Busani L, Tavirani MR, Zali MR. Prevalence of gluten-related disorders in Asia-Pacific region: a systematic review. *J Gastrointest Liver Dis* 2019; **28**: 95-105 [PMID: 30851178 DOI: 10.15403/jgld.2014.1121.281.sys]
- 4 **Cummins AG**, Roberts-Thomson IC. Prevalence of celiac disease in the Asia-Pacific region. *J Gastroenterol Hepatol* 2009; **24**: 1347-1351 [PMID: 19702902 DOI: 10.1111/j.1440-1746.2009.05932.x]
- 5 **Comba A**, Eren NB, Demir E. Prevalence of celiac disease among school-age children in Çorum, Turkey. *Turk J Gastroenterol* 2018; **29**: 595-600 [PMID: 30260783 DOI: 10.5152/tjg.2018.18020]
- 6 **Singh P**, Arora S, Singh A, Strand TA, Makharia GK. Prevalence of celiac disease in Asia: A systematic review and meta-analysis. *J Gastroenterol Hepatol* 2016; **31**: 1095-1101 [PMID: 26678020 DOI: 10.1111/jgh.13270]
- 7 **Makharia GK**, Catassi C. Celiac Disease in Asia. *Gastroenterol Clin North Am* 2019; **48**: 101-113 [PMID: 30711203 DOI: 10.1016/j.gtc.2018.09.007]
- 8 **Poddighe D**, Rebuffi C, De Silvestri A, Capittini C. Carrier frequency of HLA-DQB1*02 allele in patients affected with celiac disease: A systematic review assessing the potential rationale of a targeted allelic genotyping as a first-line screening. *World J Gastroenterol* 2020; **26**: 1365-1381 [PMID: 32256023 DOI: 10.3748/wjg.v26.i12.1365]
- 9 **Megiorni F**, Mora B, Bonamico M, Barbato M, Nenna R, Maiella G, Lulli P, Mazzilli MC. HLA-DQ and risk gradient for celiac disease. *Hum Immunol* 2009; **70**: 55-59 [PMID: 19027045 DOI: 10.1016/j.humimm.2008.10.018]
- 10 **Makharia GK**, Verma AK, Amarchand R, Bhatnagar S, Das P, Goswami A, Bhatia V, Ahuja V, Datta Gupta S, Anand K. Prevalence of celiac disease in the northern part of India: a community based study. *J Gastroenterol Hepatol* 2011; **26**: 894-900 [PMID: 21182543 DOI: 10.1111/j.1440-1746.2010.06606.x]
- 11 **Dehghani SM**, Haghighat M, Mobayen A, Rezaianzadeh A, Geramizadeh B. Prevalence of celiac disease in healthy Iranian school children. *Ann Saudi Med* 2013; **33**: 159-161 [PMID: 23563005 DOI: 10.5144/0256-4947.2013.159]
- 12 **Tatar G**, Elsurer R, Simsek H, Balaban YH, Hascelik G, Ozcebe OI, Buyukasik Y, Sokmensuer C. Screening of tissue transglutaminase antibody in healthy blood donors for celiac disease screening in the Turkish population. *Dig Dis Sci* 2004; **49**: 1479-1484 [PMID: 15481323 DOI: 10.1023/b:ddas.0000042250.59327.91]
- 13 **Wang XQ**, Liu W, Xu CD, Mei H, Gao Y, Peng HM, Yuan L, Xu JJ. Celiac disease in children with diarrhea in 4 cities in China. *J Pediatr Gastroenterol Nutr* 2011; **53**: 368-370 [PMID: 21701402 DOI: 10.1097/MPG.0b013e31822a0128]
- 14 **Yuan J**, Gao J, Li X, Liu F, Wijmenga C, Chen H, Gilissen LJ. The tip of the "celiac iceberg" in China: a systematic review and meta-analysis. *PLoS One* 2013; **8**: e81151 [PMID: 24324669 DOI: 10.1371/journal.pone.0081151]
- 15 **Yuan J**, Zhou C, Gao J, Li J, Yu F, Lu J, Li X, Wang X, Tong P, Wu Z, Yang A, Yao Y, Nadif S, Shu H, Jiang X, Wu Y, Gilissen L, Chen H. Prevalence of Celiac Disease Autoimmunity Among Adolescents and Young Adults in China. *Clin Gastroenterol Hepatol* 2017; **15**: 1572-1579. e1 [PMID: 28433781 DOI: 10.1016/j.cgh.2017.04.025]
- 16 **Chen CY**, Li JN. Insufficient awareness of celiac disease in China: population-based screening is needed. *Chin Med J (Engl)* 2019; **132**: 1513-1515 [PMID: 31188159 DOI: 10.1097/CM9.0000000000000305]
- 17 **Fukunaga M**, Ishimura N, Fukuyama C, Izumi D, Ishikawa N, Araki A, Oka A, Mishiro T, Ishihara S, Maruyama R, Adachi K, Kinoshita Y. Celiac disease in non-clinical populations of Japan. *J*

- Gastroenterol* 2018; **53**: 208-214 [PMID: 28389733 DOI: 10.1007/s00535-017-1339-9]
- 18 **Saito S**, Ota S, Yamada E, Inoko H, Ota M. Allele frequencies and haplotypic associations defined by allelic DNA typing at HLA class I and class II loci in the Japanese population. *Tissue Antigens* 2000; **56**: 522-529 [PMID: 11169242 DOI: 10.1034/j.1399-0039.2000.560606.x]
 - 19 **Fukunaga M**, Ishimura N, Abe T, Takeda M, Isomura M, Kinoshita Y, Ishihara S. Serological screening for celiac disease in adults in Japan: Shimane CoHRE study. *JGH Open* 2020; **4**: 558-560 [PMID: 32782937 DOI: 10.1002/jgh3.12334]
 - 20 **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 [PMID: 32782935 DOI: 10.1002/jgh3.12352]
 - 21 **Poddighe D**, Rakhimzhanova M, Marchenko Y, Catassi C. Pediatric Celiac Disease in Central and East Asia: Current Knowledge and Prevalence. *Medicina (Kaunas)* 2019; **55** [PMID: 30642036 DOI: 10.3390/medicina55010011]
 - 22 **Zanella S**, De Leo L, Nguyen-Ngoc-Quynh L, Nguyen-Duy B, Not T, Tran-Thi-Chi M, Phung-Duc S, Le-Thanh H, Malaventura C, Vatta S, Zibera F, Mazzocco M, Volpato S, Phung-Tuyet L, Le-Thi-Minh H, Borgna-Pignatti C. Cross-sectional study of coeliac autoimmunity in a population of Vietnamese children. *BMJ Open* 2016; **6**: e011173 [PMID: 27329441 DOI: 10.1136/bmjopen-2016-011173]
 - 23 **Thammarakcharoen T**, Hirankarn N, Sahakitrungruang T, Thongmee T, Kuptawintu P, Kanonthong S, Chongsrisawat V. Frequency of HLA-DQB1*0201/02 and DQB1*0302 alleles and tissue transglutaminase antibody seropositivity in children with type 1 diabetes mellitus. *Asian Pac J Allergy Immunol* 2017; **35**: 82-85 [PMID: 27543737 DOI: 10.12932/AP0751]
 - 24 **Pham-Short A**, Donaghue KC, Ambler G, Phelan H, Twigg S, Craig ME. Screening for Celiac Disease in Type 1 Diabetes: A Systematic Review. *Pediatrics* 2015; **136**: e170-e176 [PMID: 26077482 DOI: 10.1542/peds.2014-2883]
 - 25 **Yap TW**, Chan WK, Leow AH, Azmi AN, Loke MF, Vadivelu J, Goh KL. 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 [PMID: 25799401 DOI: 10.1371/journal.pone.0121908]
 - 26 **Savvateeva LV**, Erdes SI, Antishin AS, Zamyatnin AA Jr. Overview of Celiac Disease in Russia: Regional Data and Estimated Prevalence. *J Immunol Res* 2017; **2017**: 2314813 [PMID: 28316996 DOI: 10.1155/2017/2314813]
 - 27 **Poddighe D**, Turganbekova A, Baymukasheva D, Saduakas Z, Zhanzakova Z, Abdrakhmanova S. Genetic predisposition to celiac disease in Kazakhstan: Potential impact on the clinical practice in Central Asia. *PLoS One* 2020; **15**: e0226546 [PMID: 31895924 DOI: 10.1371/journal.pone.0226546]
 - 28 **Penny HA**, Raju SA, Lau MS, Marks LJ, Baggus EM, Bai JC, Bassotti G, Bontkes HJ, Carroccio A, Danciu M, Derakhshan MH, Ensari A, Ganji A, Green PHR, Johnson MW, Ishaq S, Lebowl B, Levene A, Maxim R, Mohaghegh Shalmani H, Rostami-Nejad M, Rowlands D, Spiridon IA, Srivastava A, Volta U, Villanacci V, Wild G, Cross SS, Rostami K, Sanders DS. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. *Gut* 2020 [PMID: 33139268 DOI: 10.1136/gutjnl-2020-320913]
 - 29 **Agarwal A**, Chauhan A, Ahuja V, Makharia GK. Opportunities and challenges in the management of celiac disease in Asia. *JGH Open* 2020; **4**: 795-799 [PMID: 33102747 DOI: 10.1002/jgh3.12381]
 - 30 **Dhawan A**, Agarwal A, Mulder CJ, Makharia GK. Celiac disease in the East and the West: Bridging the gaps between the guidelines and their implementation in daily practice is mandatory. *Indian J Gastroenterol* 2019; **38**: 185-189 [PMID: 31313236 DOI: 10.1007/s12664-019-00970-7]



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