SYSTEMATIC REVIEW

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Prevalence of Gluten-Related Disorders in Asia-Pacific Region: A Systematic Review

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ABSTRACT

Background & Aims: The epidemiology of gluten-related disorders (GRDs) is still an open field to be explored. We conducted this systematic review based on the current epidemiology knowledge of GRDs, focusing on the changing prevalence of GRDs reported in the Asia-Pacific region.
Methods: We searched Medline, PubMed, Scopus, Web of Science and Cochrane database with the following MeSH terms and keywords: celiac disease (CD), wheat allergy (WA), non-celiac gluten sensitivity (NCGS), dermatitis herpetiformis (DH) and gluten ataxia (GA) and the prevalence studies published from January 1991 to January 2018. Each article was cross-referenced with "Asia-Pacific region" and countries in this region such as Australia, New Zealand, India, Pakistan, Turkey, Iran and others.
Results: We included 66 studies, which reported the prevalence of GRDs in the Asia-Pacific region. Prevalence of celiac disease was 0.32%-1.41% in healthy children and 0.05%-1.22% in the adult population, while the prevalence in the high risk population was higher (0.6%-11.8%). Previous studies have shown a very low incidence of dermatitis herpetiformis (DH) (<0.001%) and gluten ataxia (GA) in this area. Few studies on NCGS outbreaks have been found in this area due to the lack of specific diagnostic biomarkers. Wheat allergy (WA), although uncommon in most Asian-Pacific countries, is the most common cause of anaphylaxis in this region.
Conclusion: The results of this systematic review suggest the need to plan further proper epidemiological studies in order to understand the natural history of GRDs and to assess its burden on health systems.

Key words: gluten-related disorders – celiac disease – non-celiac gluten sensitivity – wheat allergy.

Abbreviations: AGA: anti-gliadin antibody; CD: celiac disease; DGP: deamidated gliadin peptides; DH: dermatitis herpetiformis; EMA: anti-endomysial antibodies; GA: gluten ataxia; GRDs: gluten-related disorders; IBS: irritable bowel syndrome; NCGS: non-celiac gluten sensitivity; SEIBDs: sub-epidermal immunobullous disorders; t-TG: tissue transglutaminase; WA: wheat allergy.

INTRODUCTION

Gluten-related disorders (GRDs) are known as an epidemic-related phenomenon that affects many people worldwide. In the 1980s, classification of GRDs was very simple, because celiac disease (CD) and dermatitis herpetiformis (DH) were the only known diseases with a well-documented role of gluten in their pathogenesis. More recently, gluten and other proteins have been recognized as a possible cause of wheat allergy (WA) [1]. In addition, the large number of patients with intestinal and extra-intestinal symptoms who are sensitive to dietary gluten without evidence of CD or WA, has contributed to the identification of a new gluten-related syndrome defined as non-celiac gluten sensitivity (NCGS) [2]. Therefore, the spectrum of GRDs covers a wide range from gastroenterology to allergy and from neurology to dermatology [3]. The classification of GRDs is presented in Fig. 1. Within the large family of GRDs, each gluten-related disorder exhibits a unique pathophysiological response to gluten ingestion, though there may be a significant overlap in clinical presentations. This overlap makes diagnosis difficult, particularly in the case of NCGS. As a result, different priorities and diagnostic tools are required for different situations.

Gluten-related disorders and questions surrounding these associations have recently attracted attention due to the high prevalence of undiagnosed cases with a large number of symptoms and complications inside and outside the small

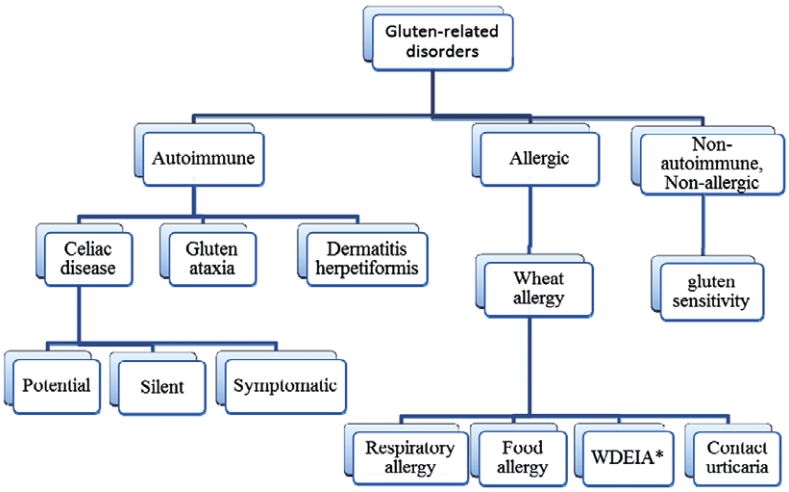


Fig.1. Classification of gluten related disorders according to the consensus conference on gluten related disorders held in February 2011[3]. *WDEIA: wheat-dependent exercise induced anaphylaxis.

intestine. Moreover, because of the development of sensitive and specific serological tests for the diagnosis of GRDs, the prevalence of the diseases has changed. Their true prevalence is underestimated and there is little information available regarding the prevalence of GRDs in the Asia-Pacific region. Therefore, we conducted a systematic review to evaluate the data concerning the epidemiology of GRDs, focusing on the changing of the reported GRDs prevalence in this region.

METHODS

We developed a protocol, including eligibility criteria, search strategies, a criteria for study selection and methods for extracting data according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [4].

Search methods

Previously published articles indexed in Medline, PubMed, Scopus, Web of Science and Cochrane database were searched using the following MeSH terms and keywords "prevalence AND gluten-related disorders", "prevalence AND Celiac disease", "prevalence AND Wheat allergy", "prevalence AND non-celiac gluten sensitivity", "prevalence AND dermatitis herpetiformis" and "prevalence AND gluten ataxia". Each one was cross-referenced with "Asia-Pacific region" and countries in this region such as Australia, New Zealand, India, Pakistan, Turkey, Iran and others. As the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) released the first guideline for diagnosis of CD in 1990 [5], we considered this year as a dividing year for well-defined diagnostic criteria for CD and other gluten-related disorder. Therefore, all relevant published articles from January 1991 to January 2018 were included in this systematic review. Searching was carried out in the English language and those studies without access to the full text were not included in this review. Moreover, conferences related to GRDs and the references lists of studies were also assessed to include further appropriate articles. Figure 2 shows the flowchart of selecting the studies based on PRISMA guidelines.

Inclusion criteria

All the studies reporting the prevalence of at least one of GRDs in the general population in Asia-Pacific region were screened. For the adult population, we included studies that reported the prevalence in general and/or high-risk population based on celiac-specific serological tests [such as anti-tissue transglutaminase (t-TG) antibodies, anti-endomysial antibodies (EMA) and deamidated gliadin peptides (DGP) antibodies] with confirmation of villous flattening at duodenum biopsies, according to the Marsh classification [6]. In children, guidelines allow the diagnosis of CD without endoscopy if t-TG levels are increased more than 10x the upper normal limits. [7]. For DH, we included studies that reported the prevalence based on serological markers and duodenal biopsy. For gluten ataxia (GA) the biopsy was not necessary for the diagnosis. To assess the prevalence of WA we included studies that used wheat specific IgE or skin prick test (SPT), without duodenal biopsy. To investigate the status of NCGS in Asian-Pacific countries according to the Salerno criteria [8], all double-blind randomized placebo controlled trials (DBRPCT) that performed the gluten re-challenge in suspected NCGS patients were considered.

Exclusion criteria

The exclusion criteria were: (a) studies documenting the prevalence based on self-reporting database or hospital registries; (b) adult population studies reporting only the sero-prevalence of CD; (c) studies reporting the CD prevalence only by anti-gliadin antibody (AGA) marker even with biopsy, because AGA is no longer recommended as a sensitive and specificity screening test for CD [7] (however, studies were included if AGA was used in combination with other celiac-specific serological tests); (d) case reports, case series and letters to the Editor; (e) studies without access to the full text and those with unclear results.

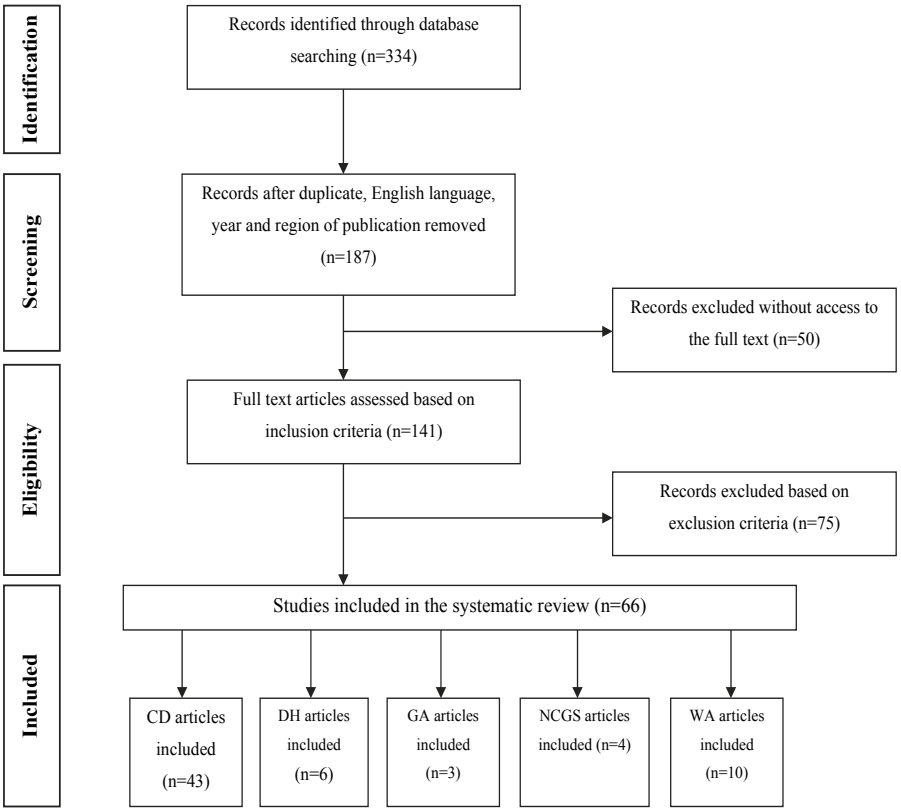


Fig. 2. PRISMA flowchart of selecting the studies

Study selection

Two authors (S.A. and M.A.P.) performed the literature search, reviewed all the full texts, and individually evaluated the articles based on pre-decided inclusion and exclusion criteria. Disagreements between the two authors were resolved by discussion. If disagreements persisted, a third author (M.R.N.) reviewed the study and made the final decision. To increase the quality of the review, a blind method was used, hiding the journal and the author names.

Data extraction

Information extracted from each study included: name of the first author, year of publication, country of origin, number of included patients and their median age, type and design of the study, diagnosis of GRDs (serological markers and/or duodenal biopsy), diagnosis of NCGS, duration of GFDs, outcome measure (prevalence %).

RESULTS

Based on our inclusion criteria, 66 articles in the English language from January 1991 to January 2018, which reported the prevalence of at least one of the GRDs in Asia-Pacific region, were chosen for this study, that included 43 articles on CD, 6 on DH, 3 on GA, 4 on NCGS and 10 on WA.

Celiac Disease (CD)

We found 19 studies reporting the prevalence of CD in healthy and and 24 studies in high-risk population in 11 Asian-Pacific countries; New Zealand, Australia, Turkey, India, Iran, Israel, Saudi-Arabia, Kuwait, Oman, China and Japan. Data are synthetized in Table I [9-26]. Prevalence of CD ranged from 0.32% to 1.41% in healthy children and from 0.05% to 1.22% in adults.

The prevalence of CD is higher in some groups of patients, having a positive family history of CD, insulin dependent diabetes mellitus type 1 (DM1), chronic diarrhea, autoimmune thyroiditis, inflammatory bowel diseases (IBD), irritable bowel syndrome (IBS), Down syndrome (DS), Turner syndrome (TS) and also in dyspeptic patients. For these categories, serological and biopsy screening is necessary [27, 28]. Data about the prevalence of GRDs in these high risk groups of patients are reported in Table II [29-52]. The reported ranges of CD prevalence were from 1% to 11.8% in high-risk children and 2.1% to 5.9% in high-risk adults. A study by Fukunaga et al. showed that the presence of CD in the healthy Japanese population was low at 0.05% and was rarely found in patients with unexplained chronic abdominal symptoms (2.1%) [52].

Dermatitis herpetiformis (DH)

In the Asia-Pacific region, DH is very rare and only a few studies reported the prevalence of DH in this area, presented in Table III [53-58].

Gluten ataxia (GA)

There are comparatively fewer reports on GA in this region (Table III) [58-61].

Non-celiac gluten sensitivity (NCGS)

Few studies reported the prevalence of NCGS in Asia–Pacific region (Table IV) [62-67].

Table I. Prevalence of celiac disease among the healthy population in Asian-Pacific countries in children and adults

	Country [Ref]	Year of study	Sample size	Mean age (Range)	Serology	Prevalence (%), n:total	CI 95%
Children	India [14]	2003-2004	4,374	10.7 (3-17)	t-TG1	(0.32), 1:310	0.15-0.49
	Turkey [9]	2005	1,263	11.9 (6-17)	t-TG1	(0.55), 1:180	0.14-0.96
	Turkey [10]	2006-2008	20,190	11.6 (16-17)	t-TG1, EMA[1,2]	(0.47), 1:212	0.38-0.56
	Iran [16]	2006-2008	634	12.8 (7-18)	t-TG1	(0.47), 1:211	0-1
	India [13]	2008-2009	3,643	10.5 (3-17)	t-TG1	(1.41), 1:71	1.03-1.79
	India [15]	2008-2009	400	5.6 (6 m-12 y)	t-TG[1,2]	(1), 1:100	0.02-1.98
	Iran [17]	2011-2013	1,500	9.5 (6-12)	t-TG1	(0.6), 1:167	0.21-099
	Saudi-Arabia [26]	2012-2014	1,141	11 (6-18)	t-TG1	(0.9), 1:114	0.35-1.45
Adults	New-Zealand [24]	2000	1,064	50.2 (36-74)	EMA[1,2]	(1.22), 1:82	0.56-1.88
	Australia [25]	2001	3,011	40 (30-50)	EMA1	(0.23), 1:430	0.06-0.40
	Israel [22]	2000-2001	1,571	40.7 (18-76)	t-TG1, EMA[1]	(0.63), 1:157	0.24-1.02
	Turkey [11]	2001-2003	2,000	33 (20-59)	t-TG1	(0.70), 1:141	0.33-1.07
	Iran [18]	2003	2,000	35.5 (18-65)	AGA1, EMA[1]	(0.60), 1:166	0.26-0.94
	Israel [23]	2003	850	18 (18)	t-TG1, EMA[1]	(0.70), 1:141	0.14-1.26
	Iran [19]	2003-2004	2,795	33.7 (18-66)	t-TG1, EMA[1]	(0.96), 1:104	0.60-1.32
	Iran [21]	2004	1,440	45.5 (20-38)	t-TG1, EMA[1]	(0.34), 1:288	0.04-0.64
	Iran [20]	2006-2007	1,600	33.2 (18-65)	t-TG1	(0.87), 1:114	0.41-1.33
	India [13]	2008-2009	6,845	34.4 (18-64)	t-TG1	(0.85), 1:118	0.63-1.07
	Turkey [12]	2011-2013	1,554	42.1 (18-82)	t-TG[1,2] DGP[1,2]	(0.39), 1:259	0.08-0.70
	Japan [52]	2014-2016	2,008	53 (25-80)	t-TG[1], EMA[1]	(0.05), 1:2008	0.01-0.2

[1]IgA, [2]IgG, EMA: Anti-endomysial antibodies; AGA: Anti-gliadin antibodies; t-TG: tissue transglutaminase; DGP: deamidated gliadin peptides, CI; Confidence intervals.

Wheat allergy (WA)

Population studies on WA in the Asia-Pacific region are shown in Table V [68-85].

DISCUSSION

In recent years, the prevalence of a wide spectrum of GRDs has increased and it can be related to changes in the global dietary habits. In the past, the prevalence of GRDs in Asia-Pacific region was underestimated due to lack of awareness of the diseases. Although today awareness of GRDs in the Asia-Pacific region has increased, there is still little information available regarding GRDs prevalence. Therefore, we conducted this systematic review to gather the comprehensive information about GRDs in this region. Map 1 shows the available data on at least one of GRDs in the Asia-Pacific region.

Over the past few years, awareness about CD has increased in Asia-Pacific, indicating by the increasing number of publications on CD in this region [86]. However, the data on the prevalence of CD is only available from a few Asian countries and some Middle East countries [87, 88]. According to the data presented in this study, the range of CD prevalence was reported from 0.23% to 1.41% and from 1% to 11.8% in healthy and high-risk population, respectively, which is similar to Western countries. In Europe and North America, the prevalence of CD in the general population is approximately 1% [89]. The prevalence of CD ranges from 2–3% in Finland and Sweden to only 0.2% in Germany [90], and this is similar to the prevalence of CD in the general population of the Asian-Pacific region. The prevalence of CD in diabetes mellitus type 1 (DM1) patients in Western countries has been reported between 1-12% [91], and is quite similar to that in the Asia-Pacific region, which reported a prevalence of CD between 2.3%-11.3% in DM1 patients [33-42]. The CD prevalence in DM1 patients was significantly higher in children compared to adults (6% vs. 2.5%; P<0.05) in the Asia-Pacific region. The National Institutes of Health (NIH) estimated the prevalence of CD among the first degree relatives in US to be 4-12% by biopsy [92]. Moreover, the prevalence of CD in first-degree relatives in Western countries is around 10% [93, 94]. The CD prevalence among first-degree relatives in the Asia-pacific region was found to be lower than in the USA and Western countries (4.4-5.1%) [47-49]. The prevalence of CD in this region shows a great heterogeneity. This heterogeneity in the Asia-Pacific region is related to highly variable factors such as the level of gluten intake and frequency of HLA-DQ2/HLA-DQ8 in the population [95]. In Asian-Pacific countries, wheat consumption also varies from as high as more than 100 kg per year per person in most of the central Asian countries such as Turkey, Iran, Saudi Arabia and Pakistan, to 50–100 kg per year per person in India, China, Australia and New Zealand and under 50 kg per year per person was estimated in Japan, Korea, Indonesia, Israel and Malaysia [96, 97]. Due to the low consumption of products containing wheat, along with a low frequency of HLA-DQ2/HLA-DQ8 in South East Asian countries, including Korea, Taiwan, Philippines and the smaller islands of the pacific, CD is still uncommon in these countries [98].

Table II. Prevalence of celiac disease among the high-risk population in Asian-Pacific countries in children and adults

	Country [Ref]	Year of study	Risk factor	Sample size	Mean age (Range)	Serology	Prevalence (%), n:total	CI 95%
Children	Australia [37]	1990-2009	DM1	4,379	6.6 (1-8)	t-TG1, EMA[1]	(4.2); 1:24	3.61-4.79
	Iran [43]	1997-2003	Chronic diarrhea	824	8.5 (3m-14y)	AGA[1], EMA[1]	(8.9); 1:15	6.9610.84
	Kuwait [34]	1998-2010	DM1	47	66 M (7-189m)	AGA[1,2] EMA[1]	(6.4); 1:15	0-13.4
	Iran [33]	2003-2004	DM1	87	11.7 (2-18)	t-TG[1], EMA[1]	(3.4); 1:29	0-7.21
	Turkey [45]	2005-2006	AT	101	12.2 (2-18)	t-TG[1]	(4.9); 1:20	0.69-9.11
	China [44]	2005-2008	Chronic diarrhea	118	(1m-18y)	t-TG[1], EMA[1]	(11.8); 1:8	5.98-17.62
	Turkey [29]	2005	DS	100	6.01 (2-14)	EMA[1]	(1); 1:100	0-2.95
	India [31]	2007-2009	DS	100	(2-18)	t-TG[1], EMA[1]	(6); 1:17	1.35-10.65
	Saudi Arabia [30]	2007-2011	DS	51	4.69 (0.57-16.64)	t-TG[1]	(2); 1:51	0-5.84
	India [47]	2008-2010	First-degree relatives	91	9.5 (3-17)	t-TG[1]	(4.4); 1:23	0.19-8.61
	Saudi Arabia [35]	2008-2010	DM1	106	8.5 (8m-16y)	t-TG[1], EMA[1]	(11.3); 1:8	5.27-17.33
	Oman [36]	2011-2012	DM1	91	10.8 (2-17)	t-TG[1]	(5.5); 1:18	0.82-10.18
	Turkey [38]	2014-2016	DM1	218	12.9 (2-18)	t-TG[1]	(5); 1:20	2.11-7.89
	Iran [41]	2000-2001	DM1	250	18.7 (2-22)	EMA[1]	(2.4); 1:41	0.50-4.30
Adults	Australia [32]	1997	DS	51	37 (25-62)	EMA[1], AGA[1]	(3.9); 1:26	0-9.21
	Turkey [39]	2005	DM1	122	-	EMA[1]	(2.4); 1:41	0-5.12
	Turkey [46]	2006-2007	AT	136	43.1 (17-65)	t-TG[1]	(5.9); 1:17	1.94-9.86
	Iran [42]	2006-2007	DM1	100	21.8 (7-50)	t-TG[1]	(3); 1:34	0-6.34
	Iran [50]	2007-2008	dyspeptic	407	36.1 (≥ 18)	t-TG[1,2]	(2.4); 1:40	0.91-3.89
	Iran [51]	2009-2015	IBS	1000	29 (10-70)	t-TG[1]	(5.7); 1:17	4.26-7.14
	India [48]	2009-2014	First-degree relatives	434	29.8	t-TG[1]	(5.1); 1:20	3.03-7.17
	Turkey [49]	2012	first-degree relatives	484	-	t-TG[1]	(4.8); 1:21	2.90-6.70
	Turkey [40]	2012-2013	DM1	425	37.6 (15-80)	EMA[1]	(2.3); 1:42	0.87-3.73
	Japan [52]	2014-2016	Abdominal symptom	47	53 (25-80)	t-TG[1], EMA[1]	(2.1); 1:47	0-6.34

[1]IgA, [2]IgG, EMA: Anti-endomysial antibodies; AGA: Anti-gliadin antibodies; t-TG: Tissue transglutaminase; DGP: deamidated gliadin peptides; DM1: Diabetes Mellitus type1; DS: Down syndrome; IBS: irritable bowel syndrome, AT: autoimmune thyroiditis; CI; Confidence intervals.

Dermatitis herpetiformis is a relatively rare disease in Asia-Pacific region, and more prevalent in Scandinavian countries and UK. Studies conducted in Scotland and Sweden found an incidence of 11.5 and 19.6 affected individuals per 100,000, respectively [99, 100]. The highest prevalence of DH ever reported is in Finland, with 75.3 affected individual per 100,000 [101]. It affects predominantly Caucasians compared to African-Americans or Asians. The only population-based study in Asia-Pacific region reported a prevalence of DH less than 0.001 per 2.5 million healthy adults in China [54].

Table III. Population studies on dermatitis herpetiformis (DH) and gluten ataxia (GA) in the Asia-Pacific region

	Country [Ref]	Year	Sample size	Biopsy	Serology	Outcomes	CI 95%
DH	Malaysia[57]	1975-1990	148 patients with bullous diseases	Yes	IgA	No cases of DH reported	-
	China [54]	1976-1985	2.5 million healthy adults	Yes	IgA	8/2.5 million (<0.001)	0.0006-0.0013
	China [53]	1985-1992	234 patients with bullous diseases	Yes	IgA, IgG, IgM, C3	6/234 (2.6%)	0.56-4.63
	China [55]	1993	24 patients with IgA deposition	Yes	NR	1/24 (4.2%)	0-12.22
	Taiwan [58]	1995-2008	16 LABD* patients	Yes	IgA, IgG, C3	8/16 (50%)	25.5-47.5
	Singapore [56]	1998-1999	67 patients with SEIBDs#	Yes	IgG, C3	No cases of DH reported	-
GA	Japan [59]	2006	14 patients with idiopathic cerebellar ataxia	-	AGA[1,2]	1/14 (7.1%)	0-20.5
	Iran [61]	2006-2007	30 patients with idiopathic cerebellar ataxia	-	AGA[1,2], AEA[1,2]	2/30 (6.7%)	0-15.64
	Japan [60]	2014	49 patients with cerebellar ataxia	-	DGP[1,2]	8/49 (8.1%)	0.46-15.73

*LABD: Linear immunoglobulin A bullous dermatosis, #SEIBDs: Subepidermal immunobullous disorders, 1IgA; [2]IgG. AEA: Anti-endomysial antibodies; AGA: Anti-gliadin antibodies; t-TG: Tissue transglutaminase.

Table IV. Population studies on non-celiac gluten sensitivity (NCGS) in the Asia-Pacific region

Country [Ref]	Year	Population (n)	Methodology	Outcomes
New Zealand [62]	1997-2001	916 healthy children	on GFD for 6 weeks	46 patients out of 916 had significant reduction symptoms with GFD; 46/916 (5.0%)
Australia [65]	2007-2008	34 adult Patients with IBS without CD (29-59 Y)	DBPC challenge 6 weeks on GFD	Significant reduction in symptoms in GFD group, 13 patients out of 34 patients in this group had reduce symptoms after GFD; 13/34 (38.2%)
Iran [66]	2011-2013	148 adult Patients with IBS (Based on Rome III criteria)	DBPC challenge 6 weeks on GFD	Worsening of intestinal symptoms with gluten compared to placebo 31 patients out of 72 IBS patients who commenced on a GFD for six weeks suffered from gluten sensitivity; 31/72 (43.0%)
India [67]	2013-2015	65 patients with IBS(Based on Rome III criteria) without CD and WA Older than 16 years	DBPC challenge 4 weeks on GFD	Significant reduction in visual analog scales (VAS) of symptomatology The patients in the gluten intervention group scored significantly higher in terms of abdominal pain, bloating, and tiredness (P<0.05), and their symptoms worsened within 1 week of the challenge.

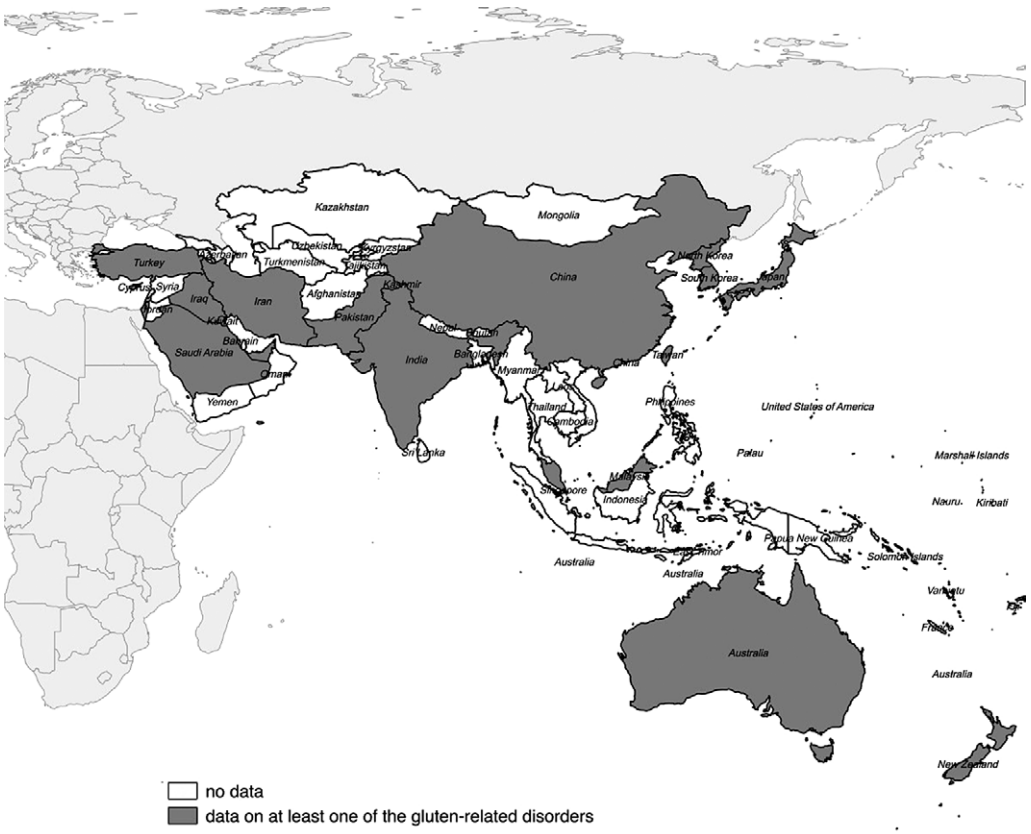
DBPC: double-blind placebo controlled, GFD: gluten free diet

Even in other countries in this region, such as Singapore and Malaysia, despite the studies on at risk populations (patients with bullous diseases), no cases have been reported [56, 57]. The characteristics of 22 Chinese patients with DH from 2006 to 2010 were assessed and compared to Caucasian populations. The clinical, histological and immune-pathological characteristics of these patients were similar to Caucasian populations, but the positive rates of anti-EMA and anti-tTG antibodies were lower compared with those seen in Western countries [102]. To date, large epidemiological studies on the prevalence of GA in Asia-Pacific region have not been published. According to the data presented in this review, the only GA prevalence was reported in patients with idiopathic cerebellar ataxia, not in the general population,

Table V. Population studies on wheat allergy (WA) in the Asia-Pacific region

Country [Ref]	Year	Population (n)	Age	Methodology	Wheat (%)	CI 95%
Australia [68]	1997-1998	620 healthy infant	0-24 months	SPT performed at 6, 12, and 24 months	1/620 (0.16%)	0-0.47
Korea [76]	2000-2006	978,146 healthy population 138 patients with anaphylaxis	0-70 years	SPT, IgE tests	6/978,146 (<0.001%) 6/138 (4.3%)	0-0.0016 0.91-7.68
Iran [69]	2003	190 children with allergy symptoms	≤ 12 years	SPT, Specific serum IgE tests	7/190 (3.7%)	1.01-6.38
Iran [69]	2003	24 children with allergy symptoms	≤ 1 years	SPT, Specific serum IgE tests	1/24 (4.1%)	0-12.03
Iran [69]	2003	63 children with allergy symptoms	1-3 years	SPT, Specific serum IgE tests	2/63 (3.1%)	0-7.38
Iran [69]	2003	39 children with allergy symptoms	3-6 years	SPT, Specific serum IgE tests	1/39 (2.5%)	0-7.40
Iran [69]	2003	64 children with allergy symptoms	6-12 years	SPT, Specific serum IgE tests	3/64 (4.6%)	0-9.73
Singapore [74]	2003-2006	413 children with allergy symptoms	≤ 12 years	SPT	13/413 (3.1%)	1.42-4.77
Iran [70]	2005-2009	69 children with history of anaphylaxis	≤ 14 years	SPT, Specific serum IgE tests	18/69 (26.1%)	22.6-29.5
Japan [78]	2009-2010	935 healthy adult	24-39 years	SPT, ω-5 gliadin IgE	2/935 (0.21%)	0-0.50
Japan [79]	2010	101,322 healthy children	0-6 years	SPT, ω-5 gliadin IgE	375/101,322 (0.37%)	0.33-0.40
Iran [71]	2012-2014	371 patients with allergy symptoms	3 m-18 years	SPT, Specific serum IgE tests	8/371 (2.1%)	0.64-3.55
Malaysia [72]	2015	Totally: 192 allergic children <2 years: 35 allergic children 2-10 years: 157 allergic children	0-10 years	Specific serum IgE tests	20/192 (10.4%) 6/35 (17.1%) 14/157 (8.9%)	6.08-14.71 4.62-29.5 4.44-13.35
Pakistan [73]	2016	689 adult allergic patients	15-73 years	self-report, SPT and OFC	By SPT: 154/689 (22.3%) By OFC: 11/101 (10.9%)	19.19-25.4 8.57-13.22

SPT: skin prick test, OFC; oral food challenge test; CI; Confidence intervals.



Map 1. The available data on at least one of the GRDs in Asia-Pacific region

and this was very low [59-61]. The low prevalence of GA in the Asian-Pacific region could be explained by incomplete experimental evidence and small sample size studies in this region, differences in genetics and nutritional habits and also by the effect of serologic tests in clinical versus research setting. To determine the exact prevalence of GA in Asia-Pacific region, further studies in other countries are necessary. Nevertheless, GA should be recognized as an important disease, causing cerebellar ataxia in Asia, despite having a lower incidence than Western countries.

For two main reasons, there is little information about the prevalence of NCGS in the Asia-Pacific region; a) there is no specific biomarker for NCGS and the diagnosis is very difficult, and b) many people make a self-diagnosis and start a GFD without medical advice or consultation [103]. Double-blind placebo controlled (DBPC) approach using 8 gr of gluten is presented as gold standard for the exact scientific identification of real cases based on "Salerno criteria" [104]. Patients frequently refuse to re-introduce gluten into their diet due to the re-occurrence of symptoms. However, according to the most recent data, NCGS is not an uncommon disorder. Prevalence rates of NCGS differed widely from 0.5% to 14% in different countries [105, 106]. There is not much information about the prevalence of NCGS in the Asia-Pacific region. We found only 4 NCGS studies in this area [62, 65-67]. In all studies, the DBPC challenge has been used as a gold standard for the detection of NCGS cases and all cases had significant reduction of symptoms with GFD. In a recent meta-analysis by Lionetti et al., the prevalence of NCGS after gluten re-challenge was low and the percentage of relapse after a gluten and placebo challenge was similar [107].

The prevalence of WA has dramatically increased in recent years in the Asia-Pacific region. Unfortunately, reports on WTA prevalence in Asia-Pacific are limited and epidemiologic studies in the general population or among children are very few. Wheat allergy, although uncommon in most Asian-Pacific countries, is the most common cause of anaphylaxis in this region [70, 76]. Wheat allergy among the adult allergic patients in Pakistan and India (22%) was the predominant type of allergy [73, 108]. A large recent review [109] found that the overall prevalence of food allergy in Asia-Pacific is fairly comparable to that in the West, although this kind of allergies differs in order to relevance in the consumption of type of food. In Japan, similar to Germany and Finland, WA has been reported as the third most common allergen after milk and egg allergy [110]. According to previous studies in Western countries, the prevalence of WA was reported to be about 1% (0.4%–4%) in the general population [111-113]. While a study from the USA reported a prevalence of WA in patients with food allergies between 11% and 20% in children, and 25% in adults [114]. The studies from Asia-Pacific region indicate that the prevalence of WA widely ranges from 0.16% to 26.1%. This heterogeneity of WA prevalence depends on whether the studies have been conducted on the healthy general population or subjects with allergy symptoms. Studies on healthy population and subjects with allergy symptoms showed that the prevalence of WA ranges from 0.16 to 0.37% and from 10.4% to 26.1%, respectively.

CONCLUSIONS

The prevalence of GRDs in Asia-Pacific region shows a great heterogeneity. Despite the improvement in diagnostic tests

for CD, it is difficult to distinguish GRDs based on a clinical presentation. Diagnostic tests for WA are unsatisfactory, and no specific biomarkers or objective diagnostic criteria have been identified for the diagnosis of NCGS. Therefore, further studies are required to determine the exact prevalence of GRDs in Asia-Pacific region.

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