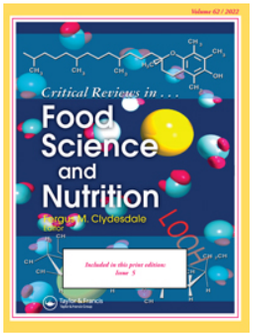

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REVIEW

Wheat consumption and prevalence of celiac disease: Correlation from a multilevel analysis

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ABSTRACT

Celiac disease (CD) is triggered by both genetic and environmental factors. More than 1% of the world's population is affected by CD. In recent years, studies have confirmed a worldwide rising trend in CD prevalence. "Westernized diet" is one of the main factors of this increasing prevalence. However, the relationship between wheat consumption, its dynamics, and CD has not been adequately investigated on a global scale. This study aimed to perform a multilevel analysis of the association between wheat consumption and CD. Wheat consumption data from countries and continents were obtained from the database. The relative increase/decrease in wheat consumption over a long period (since 1961) and a short period (since 2004) were calculated using various statistical tools. The relationship between wheat consumption and celiac frequency was determined using the R-commander R package version 2.6-2. Pearson's correlation coefficient ($r = 0.88$) confirmed a high positive correlation between wheat consumption and the prevalence of biopsy-proven CD by estimating continent-wide wheat consumption data, but an insignificant correlation was found when the data were compared country-wide.

KEYWORDS

celiac disease; correlation; prevalence; wheat consumption

Introduction

Celiac disease (CD) is one of the most common genetic diseases (Gujral, Freeman, and Thomson 2012), causing a permanent intolerance to gluten in wheat and gluten-like proteins in rye, barley, and oat (Wieser and Koehler 2008; Malalgoda and Simsek 2017). Although CD was first recognized in the 20th century (Navarro et al. 2017), it continues to attract increasing attention as a common cause of morbidity. Since the end of the 20th century, the incidence of CD has been rising significantly worldwide (Ludvigsson et al. 2013; Grode et al. 2018; King et al. 2020).

CD has a global distribution, and at least 1% of the world's population is affected by CD. However, the prevalence of CD varies with geographical location (Peña and Rodrigo 2015; Singh et al. 2018). CD is prevalent not only in Europe, North and South America, and Australia, but is also common in the Middle East, Asia, and North Africa, where it was considered extremely rare until a few years ago (Barada et al. 2010; Catassi, Gatti, and Lionetti 2015). In a systematic review and meta-analysis of the global prevalence of CD, Singh et al. (2018) reported celiac prevalence between 0.05% and 2.6% in different parts of the world. It is hypothesized that the factors contributing to this difference are likely genetic and environmental factors, including wheat consumption patterns (Catassi, Gatti, and Fasano 2014; Lionetti et al. 2015; Ludvigsson and Lebwohl 2020). Several moderate-scale clinical trials have demonstrated an association between wheat gluten intake and CD. Higher gluten intake during the first 5 years of life was associated with a statistically significant increase (6 – 7%) in CD prevalence among genetically predisposed children (Aronsson et al. 2019). A higher prevalence of CD has been found in the northern part of India and China because of significant differences in dietary grain consumption (Ramakrishna et al. 2016; Yuan et al. 2017). CD prevalence is expected to increase in many developing countries due to an increase in the "westernized" diet, which includes increased wheat production and consumption (Cummins and Roberts-Thomson 2009; Catassi, Gatti, and Fasano 2014; Parra-Medina et al. 2015). Several studies have been conducted to determine the

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association between wheat intake and CD (Cummins and Roberts-Thomson 2009; Lionetti and Catassi 2014; Lionetti et al. 2015). However, the analysis did not find any statistically significant relationships. Therefore, we decided to analyze this topic by assessing not only the instantaneous consumption of wheat but also its dynamics, and to examine the correlation between wheat consumption and the prevalence of CD by countries and continents.

The aim of this study was to perform a multilevel analysis of the association between wheat consumption and CD. First, we estimated the global prevalence of CD. Second, we calculated the average wheat consumption per capita per year in different countries and continents, including consumption dynamics over the period under analysis. Third, we assessed the association between wheat consumption and CD prevalence.

Methods

The prevalence of CD

Literature search strategy

We performed a pilot study of all-accessible for us databases aiming to select the ones offering the greatest number of relevant to the topic records. As the result of the pilot study we selected PubMed, Taylor & Francis, and Google Scholar databases and conducted advanced search for full-text articles published between 2005 and 2020 using the keywords: "celiac disease" or "celiac" + "prevalence" or "incidence" or "frequency" or "screening" to identify articles describing the prevalence of CD. We did not apply any language restrictions to the articles.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for articles were determined by the objectives of our study and analysis of earlier published studies (Parra-Medina et al. 2015; Singh et al. 2018). We included studies describing clinical trials in which: (1) the prevalence of CD in the general population, healthy adults, or children was reported; (2) CD was diagnosed based on histological findings of the duodenal biopsy specimens; (3) children were included in the statistical analysis as patients with CD without biopsy, if results of serological tests (detection of IgA anti-tissue transglutaminase (tTG) and/or IgA anti-endomysium antibodies (EMA), and HLA class II antigens (HLA-DQ2 and/or HLA-DQ8 genetic markers of susceptibility)) met the requirements of the revised diagnostic guidance for pediatric CD of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (Husby et al. 2012).

Additionally, studies in which less than 50% of individuals identified as having CD by serological tests agreed to undergo a biopsy, or individuals who did not undergo a biopsy after positive serology were included in the data tables to calculate sero-prevalence but were not included in the statistical analysis of patients with CD.

Data on CD prevalence, based on a national database or hospital registry, were included only in compiling a CD distribution map, but not in the statistical analysis.

The exclusion criteria were as follows: (1) all studies describing clinical trials conducted until the year 2000; (2) clinical trials that examined people with increased risk for the development of CD: patients with other diseases (diabetes, autoimmune disorders, Down syndrome, etc.) or first-degree relatives of CD patients; (3) studies based on the client's own survey on CD diagnosis; and (4) review articles.

Data collection process

The details of the study selection process are presented in the flowchart (Supplementary Figure S1). The data from selected studies, reviewed by the coauthors, were collected by the author VB and are summarized in tables. Geographical maps of CD prevalence were created based on the obtained data using an interactive tool (https://mapchart.net/).

Wheat consumption

Continent and country-wise wheat consumption data were obtained from the Food and Agriculture Organization of the United Nations (FAO) database (http://www.fao.org) as the average wheat consumption per person per year (kg) during February 2021.

To analyze the dynamics (decrease or increase) of long-term wheat consumption, we collected the earliest available data on wheat consumption by individual continents from 1961 to 2018. We collected data on wheat consumption by individual countries from 2004 to 2018 and used data from both countries and continents to assess short-term dynamics of wheat consumption and to evaluate the correlation between wheat consumption and the prevalence of CD. The average wheat consumption per person per year (kg) from 2004 to 2018 was calculated to compare wheat consumption data during the analysis period by country and continent. A wheat consumption geographical map was created using the results of the comparative analysis.

To estimate the long-term dynamics of wheat consumption (decrease or increase), we calculated the ratio between the most recent 10-year (2008–2018) average wheat consumption and the earliest available on FAO 10-year (1961–1971) average wheat consumption. To estimate the dynamics of wheat consumption (decrease or increase) during the analyzed period of CD prevalence, we calculated the ratio between the most recent 5-year (2014–2018) average wheat consumption (short-term) and the earliest 5-year (2004–2008) average wheat consumption by continent and country.

Statistical analysis

Wheat consumption data and pooled data on CD prevalence were calculated and visualized using Microsoft Excel 2013 spreadsheet.

The correlation between wheat consumption and CD frequency was determined using R-commander (R package version 2.6-2. Institute for Statistics and Mathematics of the University of Economy, Vienna, Austria (https://cran.r-project.org/)). The Shapiro-Wilk normality test was performed, and Pearson's correlation was calculated to evaluate possible relationships. Bartlett's test was used to assess the homogeneity of variance. Welch test and one-way analysis of variance (ANOVA) were used to assess the incidence of CD in children and adults and to establish the difference between serological tests. A one-sample t-test was used to determine the 95% confidence intervals. Statistical significance was declared at pairwise two-sided p values of $p < 0.05$.

Results

Prevalence of CD in different continents

A total of 1291 records were found by conducting an advanced search on PubMed, Taylor & Francis, and Google Scholar databases (Supplementary Figure S1). After removing duplications, 434 records remained. A total of 302 records were excluded after screening the titles and abstracts. An additional 12 articles were identified through reference tracking and internet search, and finally, the full texts of 144 articles were assessed. After screening the full text, 75 articles remained, of which 70 clinical trial studies were included in the analysis of CD sero-prevalence, of which 54 studies were included in the statistical analysis of CD prevalence, and an additional five studies based on the national database or hospital registry analysis were used to compile a CD distribution map.

We found CD prevalence rates in a healthy population in 40 countries; 31 of them presented biopsy-based data. A large number of studies have estimated CD prevalence among blood donors, as in many countries, it is the only available source to estimate CD prevalence. Most epidemiological studies (n = 70) were carried out through the determination of specific serological markers of CD (IgA tTG and/or IgA EMA) in blood. Genetic markers (HLA-DQ characterization) were considered in only 10 studies. Most of the authors (n = 54) have included the histological findings of the duodenal biopsy specimens, based on the presence of villous atrophy and by a flat intestinal mucosa or, more recently, on the increase of epithelial lymphocytes without villous atrophy. The country-wide pooled prevalence of CD is shown in Figure 1.

The global pooled prevalence of CD

Based on the CD epidemiology literature published from 2005 to 2020, the biopsy-proven global pooled prevalence of CD was estimated to be 0.77% (95% CI, 0.50% − 0.87%, $p < 0.05$). According to data obtained from 54 studies, 197361 individuals were screened, and 1510 were diagnosed with CD. The global sero-prevalence of CD was calculated by the weight of the studies: 1.25% (95% CI, 1.02% − 1.57%, $p < 0.05$) (3222 from 256936 individuals, data from 70 studies). Anti-tissue transglutaminase (tTG) and anti-endomysial antibody (EMA) tests have been used in most clinical trials for CD screening. If both tests were used in the same country, the results were taken for analysis in the following order: based on positive results from both tests (tTG + EMA), based on positive results from EMA tests, based on positive results from tTG only.

Prevalence of CD in Europe

In total, 30 original research studies on CD were analyzed: 23 trials based on biopsy data, four trials based on sero-tests,

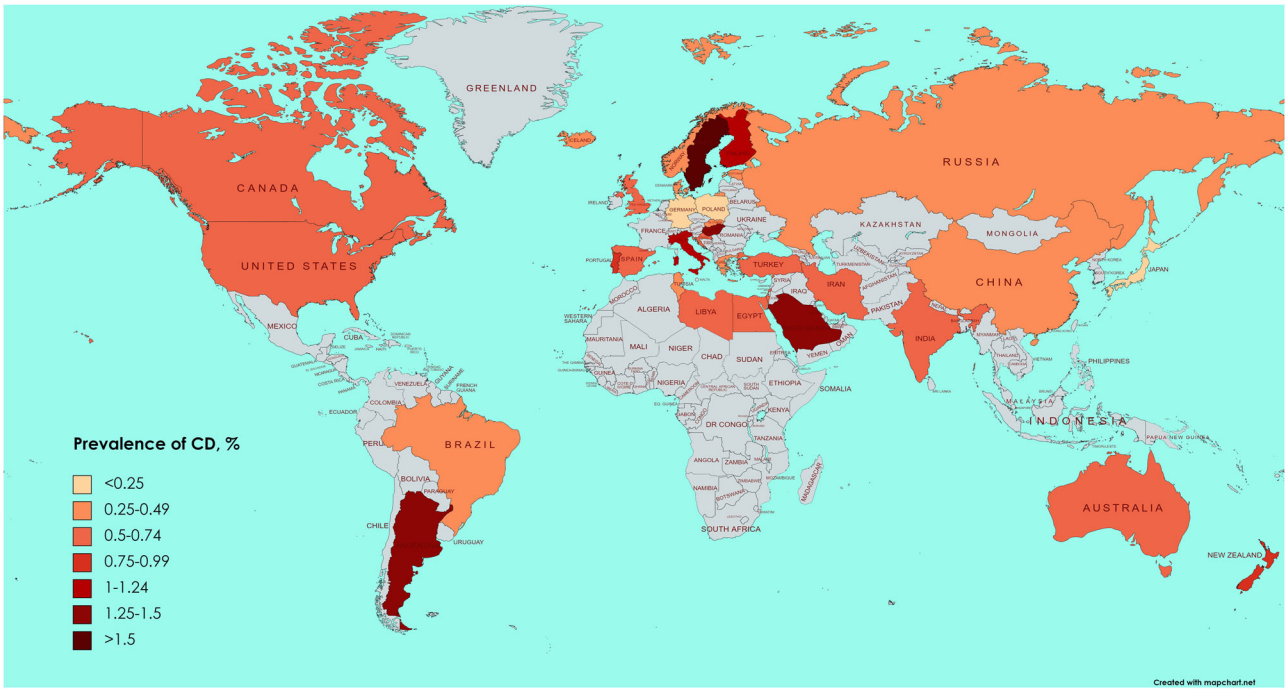


Figure 1. Country-wide pooled prevalence of CD.
Source: https://mapchart.net/

Table 1. The prevalence of CD in Europe.

Country	Sample size	Subjects	Criteria for diagnosis	Prevalence of CD by serological tests %	Prevalence of CD by biopsy % (n)	Reference
Belgium	1159	Children	tTG, EMA	0.86/0.35	ND	Vijgen et al. 2012
Croatia	1404	Children	tTG	5.6	0.5 (7)	Petricevic-Vidovic et al. 2019
Denmark	2297	Adults	tTG	2.44	0.48 (11)	Horwitz et al. 2015
	9754	General population	tGA, HLA	0.77	ND	Lund et al. 2020
Estonia	1160	Children	tTG	0.43	0.34 (4)	Ress et al. 2007
Finland	6403	Adults	tTG, EMA	2.5/2	1.33 (85)	Mustalahti et al. 2010
	2815	Adults	tTG	2.7	2.34 (66)	Vilppula et al. 2009
	3654	Children	tTG	1.42	0.25 (9)	Kondrashova et al. 2008
Germany	2157	Adults	tTG	0.65	0.37 (8)	Kratzer et al. 2013
	4173	Adults	tTG, EMA	0.5/0.3	0.14 (6)	Mustalahti et al. 2010
	12741	Children	tTG	0.9	ND	Laass et al. 2015
Greece	2230	Adults	tTG, EMA	0.18	0.18 (4)	Roka et al. 2007
	1136	Children	tTG, EMA	0.83	0.62 (7)	Karagiozoglou-Lampoudi et al. 2013
Hungary	2690	Children	tTG	1.79	1.38 (37)	Korponay-Szabó et al. 2007
Iceland	813	Adults	tTG	0.74	0.49 (4)	Johannsson et al. 2009
Italy	2645	Children	tTG, EMA	1.3/1.1	0.72 (19)	Mustalahti et al. 2010
	4781	Adults	tTG, EMA	1.4/0.70	0.50 (24)	Mustalahti et al. 2010
	4570	Children	tTG, EMA, HLA ESPGHAN criteria 2012	5.62	1.58 (72)	Gatti et al. 2020
	4048	Children	tTG,	1.26	1.16 (47)	Bonamico et al. 2011
	1002	General population	tTG, EMA	1.3	1.0 (10)	Menardo et al. 2006
Latvia	1444	Adults	tTG, EMA	0.49/0.35	ND	Leja et al. 2015
Norway	797360	Children	Norwegian Patient Register	ND	0.38 (3006)	Størdal et al. 2013
Poland	3235	Children	EMA	0.8	0.22 (7)	Szaflarska-Poplawska et al. 2009
Portugal	536	Teenagers	tTG, EMA	2.05/0.75	0.75 (4)	Antunes et al. 2006
Russian Federation	1740	Adults	tTG, EMA	2.4	0.52 (9)	Stroikova et al. 2006
	1988	Children	tTG	0.60	0.20 (4)	Kondrashova et al. 2008
Slovakia	5412000	General population	Number of patients with CD	0.27	0.25 (14500)	Kabátová 2016
Spain	2215	Adults	tTG	0.63	0.27 (6)	Novo et al. 2007
	4230	General population	tTG, EMA	0.5	0.49 (21)	Mariné et al. 2011
	198	Children	tTG	3	2.5 (6)	Almazán et al. 2015
Sweden	7567	Children	tTG, EMA	3.6	2.9 (217)	Myléus et al. 2009
	5712	Children	tTG, EMA	3.07	2.2 (123)	Ivarsson et al. 2013
United Kingdom	4566240	General population	Clinical practice research data	0.24	0.24 (10872)	West et al. 2014
	1975	Children	tTG, EMA	1.0/0.9	0.66 (13)	Mustalahti et al. 2010
Europe	**77374**				**1.07 (830)**	

CD, celiac disease; ND, no data; biopsy, not performed; tTG, anti-transglutaminase antibody; EMA, anti-endomysium antibody; HLA, human leukocyte antigen.

and three studies on registered CD patients (Table 1). The data represented 19 European countries, 15 of which provided biopsy-based research results. The pooled prevalence of CD in Europe, based on 27 clinical trials, was 1.07% (830 of 77374 individuals). The highest prevalence of CD was found in Sweden (2.56%), slightly lower in Hungary (1.38%), Finland (1.24%), and Italy (1.01%). CD is less than 1% in other European countries, as determined by biopsy. CD was occasionally diagnosed in Greece (0.18%), Germany, and Poland (0.22%).

Prevalence of CD in Asia

There were 24 CD prevalence-related articles from 11 Asian countries. Seven Asian countries provided biopsy-based data and met the inclusion criteria. The pooled prevalence of biopsy-proven CD in Asia was 0.69% (349 individuals from 50661, 16 clinical trials) (Table 2). The prevalence of CD was high in Saudi Arabia (1.42%), Israel (0.7%), Iran (0.64%), India (0.64%), and Turkey (0.53%). In other countries, the prevalence of CD was less than 0.5% (Figure 1), with the lowest prevalence in China (0.35%) and Japan (0.05%).

Prevalence of CD in American continents

Fourteen scientific articles met the inclusion criteria for North America (n = 4) and South America (n = 10). Ten of these articles were suitable for the statistical analysis. The prevalence of CD in North America was 0.53% (161 biopsy-proven individuals from 33926), with a similar prevalence of CD in the United States (0.54%) and Canada (0.52%) (Table 3). The prevalence of CD in South America was 0.49% (84 individuals from 17285). The highest prevalence was found in Argentina (1.26%) and the pooled prevalence in Brazil (0.37%), while biopsy-based studies were lacking in other countries.

Prevalence of CD in Africa, Australia and New Zealand

Africa contingent was represented by a relatively small number of articles (n = 5) on CD prevalence, all of which were biopsy-based studies. The pooled prevalence of CD in Africa was 0.42% (60 individuals from 14188) (Table 4), which was determined based on data from three countries (Egypt, Libya, and Tunisia).

Data on CD prevalence in Australia and New Zealand were presented in two articles; the estimated total CD prevalence was 0.66% (26 individuals from 3927) (Table 4).

Table 2. Prevalence of CD in Asia.

Country	Sample size	Subjects	Criteria for diagnosis	Prevalence of CD by serological tests %	Prevalence of CD by biopsy % (n)	Reference
China	19778	Adolescents and young adults	tTG / HLA	2.19/0.06	ND	Yuan et al. 2017
	2277	Adults	tTG, EMA, HLA	1.27	0.35 (8)	Zhou et al. 2020
India	2879	General population	tTG	1.44	1.08 (31)	Makharia et al. 2011
	4347	Children	tTG	0.48	0.32 (14)	Sood et al. 2006
	400	Children	tTG	1.25	1.0 (4)	Bhattacharya, Dubey, and Mathur 2009
	23331	Adults	tTG, HLA	0.73	ND	Ramakrishna et al. 2016
Iran	2799	Adults	tTG, EMA	0.96	ND	Akbari et al. 2006
	1600	Adults	tTG	0.88	0.75 (12)	Bahari et al. 2010
	1506	Children	tTG	2.00	0.60 (9)	Dehghani et al. 2013
	634	Children	tTG	0.5	0.50 (3)	Farahmand et al. 2012
Israel	850	Adults	tTG	1.1	0.7 (6)	Israeli et al. 2010
Jordan	1985	Children	tTG, EMA	0.8	ND	Nusier et al. 2010
Japan	2008	Adults	tTG, EMA	8.02/0	0.05 (1)	Fukunaga et al. 2017
	2055	Adults	tTG	0.19	ND	Fukunaga et al. 2020
Saudi Arabia	1167	Children	EMA	2.23	ND	Aljebreen et al. 2013
	1141	Children	tTG	2.8	0.88 (10)	Al Hatlani 2015
	7930	Children	tTG	2.8	1.5 (119)	Al-Hussaini et al. 2017
Turkey	20190	Children	tTG, EMA	1.34/1.06	0.47 (95)	Dalgic et al. 2011
	1730	Children	tTG	0.46	0.46 (8)	Comba, Eren, and Demir 2018
	1263	Children	tTG	0.87	0.63 (11)	Ertekin et al. 2005
	906	Adults	tTG	5.7	0.99 (9)	Gursoy et al. 2005
	1000	Children	tTG	1.0	0.9 (9)	Demirçeken et al. 2008
United Arab Emirates	1197	Adults	tTG	1.17	ND	Abu-Zeid et al. 2014
Vietnam	1961	Children	tTG, EMA, HLA	1.07/0/0.36	ND	Zanella et al. 2016
Asia	**50661**				**0.69 (349)**	

CD, celiac disease; ND, no data; biopsy not performed; tTG, anti-transglutaminase antibody; EMA, anti-endomysium antibody; HLA, human leukocyte antigen.

Table 3. Prevalence of CD in American continents.

Country	Sample size	Subjects	Criteria for diagnosis	Prevalence of CD by serological tests %	Prevalence of CD by biopsy % (n)	Reference
Canada	3850	Adults	tTG, EMA	0.88	0.52 (20)	Katz et al. 2011
United States of America	7798	General population	tTG, EMA	0.71	0.71 (55)	Rubio-Tapia et al. 2012
	22278	General population	Data tables	0.69	0.48 (106)	Kim et al. 2016
	14701	General population	tTG, EMA	0.79	ND	Mardini, Westgate, and Grigorian 2015
Colombia	228	Adults	tTG, EMA, HLA	1.32	ND	Paredes-Echeverri et al. 2020
Argentina	2219	Children	tTG, EMA	1.62/1.3	1.26 (28)	Mora et al. 2012
	144	General population	tTG, EMA, HLA	2.1	ND	Vázquez et al. 2015
Brazil	4000	Adults	tTG, EMA, HLA	0.60	0.35 (14)	Alencar et al. 2012
	2086	Adults	tTG	0.29	0.24 (5)	Pereira et al. 2006
	3000	Adults	tTG/EMA	0.8/0.5	0.37 (11)	Melo et al. 2006
	3000	Adults	tTG	1.5	0.47 (14)	Oliveira et al. 2007
	946	Elderly	tTG, EMA, HLA	0.95/0/0.32	0.11 (1)	Almeida et al. 2013
	2034	Children		ND	0.54 (11)	
Cuba	595	Children	tTG	1.18	ND	Galván et al. 2010
Mexico	1009	Adults	tTG	2.67	ND	Remes-Troche et al. 2006
North America	**33926**				**0.53 (161)**	
South America	**17285**				**0.49 (84)**	

CD, celiac disease; ND, no data; biopsy not performed; tTG, anti-transglutaminase antibody; EMA, anti-endomysium antibody; HLA, human leukocyte antigen.

Comparison of wheat consumption by continents and countries

During the period of 2004–2018, the average global wheat consumption per capita per year was 66.09 kg. Considerable continent-wide variation was noted in Africa (ranging from 49.03 kg), South America (57.01 kg), and Europe (110 kg) (Table 5). We observed great country-wide differences in wheat consumption in some countries like Japan (43.98 kg), Brazil (52.64) or Turkey (180.64 kg) and Tunisia (200.29 kg) (Table 6). The heterogeneity of wheat consumption in various countries and continents is shown in Figure 2.

Wheat consumption continent-wide dynamics (decrease or increase) from 1961 to 2018 were analyzed. The results are presented in Figure 3, and the calculated relative changes are listed in Table 5.

During the long-term period starting from 1961, wheat product consumption increased mostly in Asia (1.87-fold) and Africa (1.58-fold), and the decrease was mostly noticed in Australia and New Zealand (1.27-fold) and Europe (1.16-fold).

Table 4. Prevalence of celiac disease in Africa, Australia and New Zealand.

Country	Sample size	Subjects	Criteria for diagnosis	Prevalence of CD by serological tests %	Prevalence of CD by biopsy % (n)	Reference
Egypt	1500	Children	tTG, EMA	0.93/0.53	0.53 (8)	Abu-Zekry et al. 2008
Libya	2920	Children	tTG, EMA	1.7/0.68	0.65 (19)	Alarida et al. 2011
Tunisia	6286	Children	tTG, EMA	2.2/0.64	0.41 (26)	Hariz et al. 2007
	2064	Children	tTG, EMA	0.34	0.24 (5)	Hariz et al. 2013
	1418	Adults	tTG, EMA	0.21	0.14 (2)	Bdioui et al. 2006
Australia	3011	Adults	tTG	1.56	0.56 (17)	Chin et al. 2009
New Zealand	916	Children	Doctor-diagnosed CD	ND	0.98 (9)	Tanpowpong et al. 2012
Africa	**14188**				**0.42 (60)**	
Australia and New Zealand	**3927**				**0.66 (26)**	

CD, celiac disease; ND, no data; biopsy not performed; tTG, anti-transglutaminase antibody; EMA, anti-endomysium antibody.

Table 5. Wheat consumption and pooled CD prevalence according continents.

Continents	Wheat consumption per capita per year 2004-2018, kg	Wheat consumption increase/decrease over 2004-2018*	Wheat consumption increase/decrease over 1961-2018**	The prevalence (biopsy proven) of CD, (95% CI, $p < 0.05$)
Europe	110.00	1.035	0.861	1.07 (0.86-1.35)
Asia	63.20	1.021	1.873	0.69 (0.56-0.85)
N.America	81.54	0.952	1.165	0.53 (0.43-0.66)
S.America	57.01	1.028	1.125	0.49 (0.40-0.61)
Africa	49.03	1.055	1.582	0.42 (0.34-0.52)
Australia + New Zealand	72.88	1.126	0.785	0.66 (0.53-0.82)
Correlation with CD prevalence	$r = 0.88$, $p < 0.05$	$r = 0.10$, $p > 0.05$	$r = -0.39$, $p > 0.05$	

CD, celiac disease.
*Ratio between the average wheat consumption during the last five years (2014-2018) available on the FAO database and the period of 2004-2008 by continent.
**Ratio between the average wheat consumption during the last 10 years (2009-2018) available on the FAO database and the earliest FAO data (1961-1971 year average) by continent.

In the last decade, the highest trend in wheat product consumption was observed in Australia and New Zealand (1.13-fold increase), while the lowest trend was observed in North America (1.05-fold decrease). Analyzing country-wide prevalence data, the highest increase in wheat consumption was observed in New Zealand (1.19-fold) and Spain (1.13-fold), while the highest decrease in wheat consumption was observed in Estonia, Canada, Denmark, and Turkey with a ratio ranging 0.67-0.88. The Country-wide wheat consumption increase/decrease and the mini-diagrams of the wheat consumption dynamics are shown in Table 6.

Correlation between wheat consumption and the prevalence of CD

We performed a multilevel analysis to assess the association between wheat consumption and CD prevalence. We found a high positive correlation ($r = 0.88$, $p < 0.05$) between wheat consumption and the prevalence of CD (biopsy-proved) by estimating data by continent (Figure 4), but a non-significant correlation was found ($r = -0.036$; $p > 0.50$) when the data were compared by country (Figure 5).

We examined the associations between the relative increase/decrease in wheat consumption in the long and short term and CD prevalence by continent. Statistical analysis showed a direct correlation between short-term wheat consumption increase/decrease ($r = 0.10$) and CD prevalence, and a negative correlation ($r = -0.39$) between increase/decrease in long-term wheat consumption and CD, but the differences were not significant in either case ($p > 0.5$).

The relationship between changes in wheat consumption and the prevalence of CD was assessed by country in the short term only; however, the correlation was not significant ($r = 0.10$, $p > 0.5$).

Since the wide spread of CD prevalence rates among countries might have been due to age group differences, we investigated whether these differences were significant. The one-way ANOVA test showed a significant difference ($p < 0.05$) in the prevalence of CD among children, adults, and the general population. The prevalence of biopsy-proven CD was found among children 0.975 ± 0.664 according to data from 12 countries, compared to among adults 0.403 ± 0.207 (data from eight countries), and CD in the general population was 0.604 ± 0.282 (data from 11 countries) (Supplementary Figure S2).

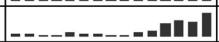
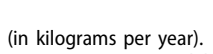
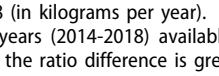
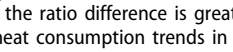
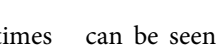
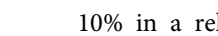
Discussion

In this study, we performed a multilevel analysis to assess the association between wheat consumption and CD prevalence. We estimated the global prevalence of CD by comparing average wheat consumption data per capita per year by country and continent, including consumption dynamics over the period under analysis, and assessed the associations between wheat consumption and the prevalence of CD.

The global prevalence of CD

Our study showed that the biopsy-proven global pooled prevalence of CD was 0.77% (95% CI, 0.50% – 0.87%, $p < 0.05$), with the highest prevalence in Europe (1.07%) among continents and in Sweden (2.56%) among countries. The global prevalence of CD by serological tests was 1.25%

Table 6. Wheat consumption and pooled CD prevalence in different countries.

Country	Wheat consumption per capita per year 2004-2018, kg*	Wheat consumption Increase/decrease**	Diagram of wheat consumption dynamics for 2004-2018***	The prevalence of celiac disease, %	Populiation
Croatia	104.47	1.03		0.5	A
Denmark	97.36	0.864		0.48	C
Estonia	80.47	0.667		0.34	A
Finland	78.24	0.906		1.24	C
Germany	84.38	1.07		0.22	B
Greece	124.67	1.032		0.33	B
Hungary	108.41	0.999		1.38	A
Iceland	70.17	1.037		0.49	B
Italy	146.53	1.001		1.01	C
Poland	107.61	0.981		0.22	A
Portugal	91.95	0.948		0.75	A
Spain	82.58	1.13		0.5	C
Sweden	81.08	1.049		2.56	A
United Kingdom	99.89	1.059		0.66	A
China	64.61	0.95		0.35	B
India	59.31	1.037		0.64	C
Iran	154.74	0.996		0.64	C
Israel	115.3	0.941		0.7	B
Japan	43.98	1.022		0.05	B
Russian Federation	133.67	1.047		0.35	C
Saudi Arabia	93.05	1.112		1.42	A
Turkey	180.64	0.881		0.53	C
Argentina	99.49	1.037		1.26	A
Brazil	52.64	1		0.37	C
Canada	81.68	0.836		0.52	B
United States of Americ	81.54	0.965		0.54	C
Australia	71.42	1.114		0.56	B
New Zealand	80.39	1.187		0.98	A
Egypt	144.63	1.026		0.53	A
Libya	121.81	1.12		0.65	A
Tunisia	200.29	1.026		0.34	C

A, children; B, adults; C, general population.
*Country-wide average wheat consumption per capita from 2004 to 2018 (in kilograms per year).
** Ratio between the average wheat consumption during the last five years (2014-2018) available in the FAO database and the period of the first five years (2004-2008) by country. The icons show an increase/decrease (□) when the ratio difference is greater than 5%.
***Diagram of wheat consumption dynamics for 2004-2018 visualizes wheat consumption trends in every country during 15 years period.

(95% CI, 1.02% − 1.57%, $p < 0.05$). CD occurred 2.42 times more often among children than among adults.

Our study results confirmed earlier findings (Ludvigsson et al. 2013; Grode et al. 2018; Gatti et al. 2020; King et al. 2020; Wieser, Koehler, and Scherf et al. 2020), showing exponential growth in CD prevalence worldwide. A recent meta-analysis by Singh et al. (2018), which was based on studies up to 2016, showed a 0.7% global biopsy-proven pooled CD prevalence; the highest prevalence among continents was also found in Europe. Compared to our results, it can be seen that the global CD prevalence has increased by 10% in a relatively short time (four years). The increasing prevalence of CD is also found by comparing the results by continent: from 0.8% to 1.07% in Europe, from 0.4% to 0.49% in South America, and from 0.6% to 0.69% in Asia. Meanwhile, data in North American countries remained similar, while the prevalence of CD in Africa was lower (0.42% vs. 0.5%). We found a slightly higher prevalence of CD (0.69% vs. 0.6%) in Asia and Oceania, as confirmed by a recent study by Ashtari et al. (2021).

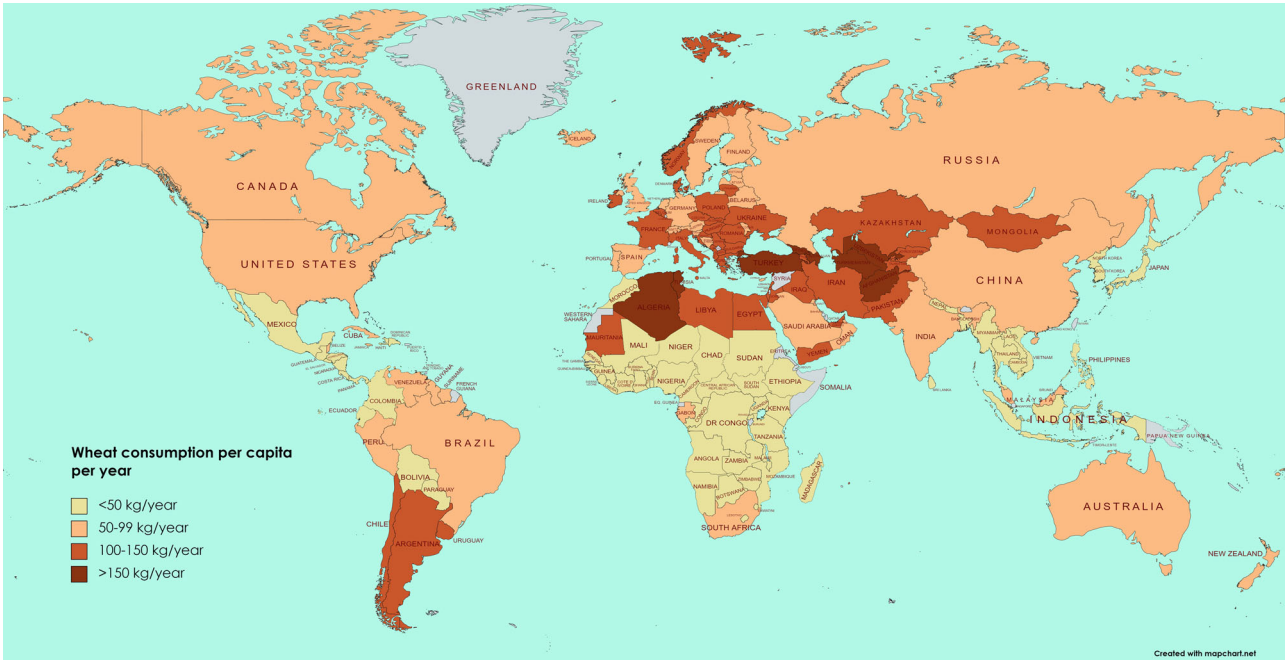


Figure 2. Country-wide average wheat consumption per capita from 2004 to 2018 (in kilograms per year).
Source: https://mapchart.net/

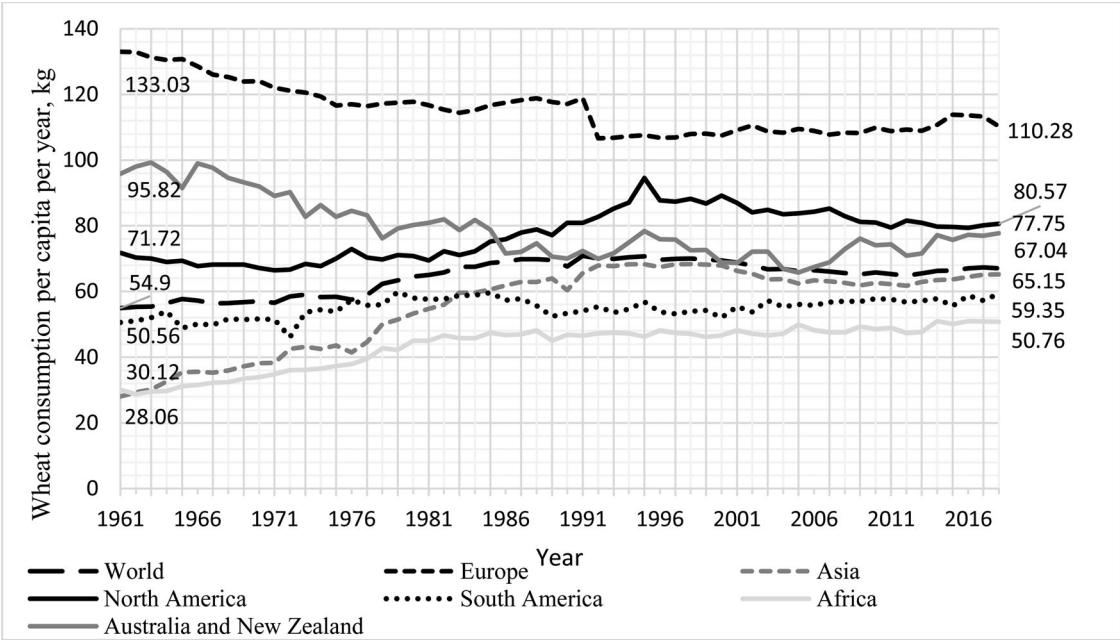


Figure 3. Wheat consumption per capita 1961–2018 by continent (in kilograms per year).

Although our study did not investigate other factors influencing the increase in CD prevalence rates, the results of the scientific literature analysis suggest that it could be related to recent changes in environmental conditions, for example, it is related not only to the amount of wheat consumed, but also to the quantity and quality of ingested gluten (Kasarda 2013), dough fermentation (Moroni, Dal Bello, and Arendt 2009; Boukid et al. 2017), infections (Scherf et al. 2020), human intestinal microbiome (Valitutti, Cucchiara, and Fasano 2019; Chibbar and Dieleman 2019), patterns of infant nutrition (Ivarsson et al. 2013; Chmielewska et al. 2015; Aronsson et al. 2019), and prominent genetic risk (HLA-DQ2/DQ8) (Sollid et al. 2012; Sharma et al. 2016; Martina et al. 2018). This rise may have been due to a real increase in the incidence of CD during the last decades, also this trend can be partially explained by progress in understanding the general principles of the pathogenesis of CD (Lindfors, Koskinen, and Kaukinen 2011; Zhu, Mulder, and Dieleman 2019) and so-called "false" increase due to better diagnostics and improved awareness: higher accuracy tests and the current diagnostic algorithm (Verma et al. 2018; Anderson et al. 2013). Even though CD is now being more diagnosed clinically yet a significant part of the "celiac iceberg" remains undetected, with a ratio of

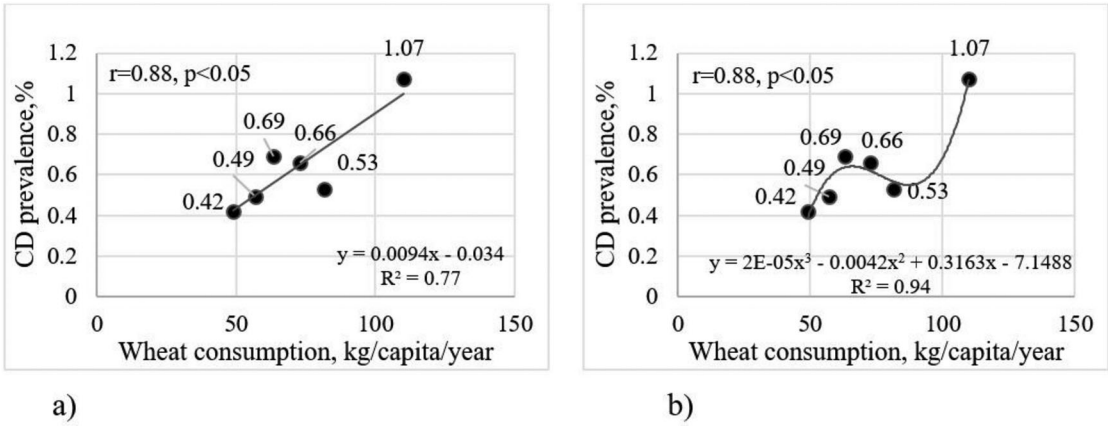


Figure 4. Correlation between wheat consumption and the prevalence of CD by continent a) linear regression trend line; b) polynomial trend line.

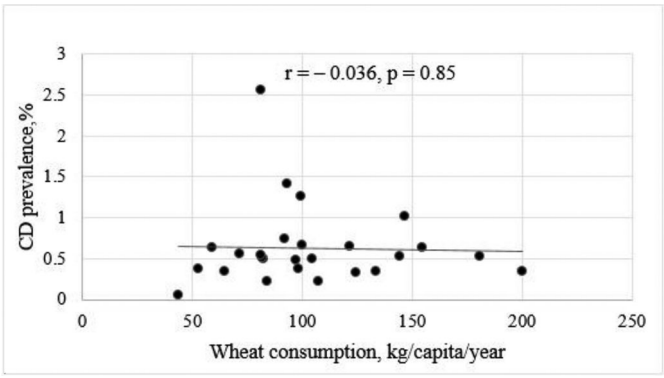


Figure 5. Correlation between wheat consumption and the prevalence of CD by country.

1:3 to 1:5 between diagnosed and undiagnosed cases (Lionetti et al. 2015; Catassi 2017; Savvateeva et al. 2017; Popp and Mäki 2019). This could have led to an underestimation of the actual CD prevalence in some countries.

CD is a multifactorial disease that can be diagnosed at any age. Our retrieved literature showed that the lowest incidence of CD was found among healthy blood donors (Bdioui et al. 2006; Novo et al. 2007; Alencar et al. 2012). We found that CD occurred 2.42-fold more often among children than among adults (0.975% children vs. 0.403%). Other studies demonstrated similar results: children were diagnosed with CD 1.65-fold more often than adults worldwide (King et al. 2020) and 2.15-fold in Asia (Ashtari et al. 2021). The difference was as much as five-fold in individual countries (Almeida et al. 2013; Mariné et al. 2011). However, in some countries, CD is more common in adults than in children. For example, in Finland, the distribution of CD is approximately 2.7% in adults and 2% in children (Vilppula et al. 2009). Although CD is becoming increasingly recognized in the elderly population (Cappello, Morreale, and Licata 2016; Zhu, Mulder, and Dieleman 2019), there is a lack of scientific articles analyzing these issues. Thus, the diversity of the methodology (some countries provided CD prevalence data among children, another on adult blood donors or elderly population) used for CD assessment might have impacted the wide spread of the results on CD prevalence in our study.

We found a CD sero-prevalence of 1.25% worldwide. CD prevalence based on serological tests was higher than that determined by biopsy, because not all individuals identified by serological tests underwent biopsy, and serological tests sometimes showed "false-positive" results. This value is lower than that reported by Singh et al. (2018) (1.4%). However, our findings did not support a decrease in the extent of CD. This could be due to the use of more accurate testing methods, as we calculated the data in this order of priority: on positive results from both tests, tTG + EMA, positive results from EMA tests, and based on results from tTG only. CD prevalence estimated with IgA-based tTG antibodies (1.67% ± 1.47%, from 59 clinical trials) was significantly higher ($p = 0.01$) than the EMA results (0.75% ± 0.51%) obtained from 30 clinical trials and that obtained by a histological diagnosis. We obtained a greater difference than the other studies that showed a positive correlation with villous atrophy in pediatric CD (70% for tTG and 74% for EMA) and high specificity (> 98%) at strongly positive antibody levels (tTG >100 units or EMA titer > 1:1280) (Alessio et al. 2012; Ho, Keenan, and Day 2020). Therefore, both of these highly sensitive tests are recommended for a more accurate diagnosis of CD (Sobhani Shahmirzadi and Sohrabi 2019), as patients with positive anti-tTG/negative EMA have a low probability (17.7%) of being affected by CD (Infantino et al. 2020).

Wheat consumption and its dynamics over the last fifty years

Cereals remain the most important food source in the world, providing more than 55% of the calories consumed worldwide (Gutiérrez et al. 2018). Wheat is a most-produced crop and a global staple food in the last century (Curtis and Halford 2014), and wheat-based food supplies up to 20% of the global population energy intake (Wieser, Koehler, and Scherf et al. 2020). The global wheat yield continued to increase and total consumption was rising over the years, but the rate of increase in total wheat consumption has slowed since the beginning of this century, and global wheat consumption per capita has decreased slightly. The contribution of wheat to energy intake varies significantly between developing and developed countries (Gutiérrez et al. 2018). Although the average wheat consumption is still the highest in Europe and increased 1.16-fold over the analyzed period (from 1961), it has remained constant or even decreased

during the last few years (Figure 3). People in Australia and New Zealand consumed significantly less wheat (1.27-fold). These changes might have been related to the fact that wheat has been the center of vigorous debate related to health and nutrition. In the last decade, wheat has gained a negative reputation. It could also be influenced by a number of pseudoscientific books and press reports, and due information and discussions about nutrition in social networks that recommended the avoidance of wheat consumption not only for those suffering from gluten intolerance, but also for healthy populations (Wieser, Koehler, and Scherf 2020). Therefore, an increasing number of individuals in Western countries have decided to adopt a gluten-/wheat-free diet (Lis et al. 2015; Kamiński et al. 2020).

Wheat consumption increased slightly in both American continents (1.12-1.17-fold). However, in other continents, wheat consumption is growing rapidly (Curtis and Halford 2014; Mottaleb, Rahut, Kruseman, and Erenstein 2018). Wheat demand is rising in Asia and Africa partly because of population growth, but also because of increasing consumption per capita in some countries. Wheat-based products, however, are becoming more common with urbanization and rising income in Asia, which were once considered traditional rice-eating regions (Zanella et al. 2016). The increase in wheat consumption was more common in Asian (1.87-fold) and African (1.58-fold) countries, with Indonesia, Bangladesh, Thailand, Vietnam, Nigeria, and Sudan, where consumption increased 14.6-269-fold from 1961 to 2018. Nevertheless, consumption is decreasing in several large countries, such as Russia and Ukraine (about 1.5-fold decrease) during this period (Curtis and Halford 2014), the greatest demand for wheat worldwide was determined by China, while the population doubled between 1961 and 2018, and wheat consumption increased 6-fold in the meantime.

Correlation between wheat consumption and the prevalence of CD

Our study confirmed a high positive correlation ($r = 0.88$, $p < 0.05$) between wheat consumption and CD prevalence in the continent (Figure 4). In the case of linear regression, a high R^2 value ($R^2 = 0.77$) was obtained (Figure 4a), which showed a high influence of wheat consumption and a low influence of other factors on CD prevalence. However, it can be seen that this correlation may not necessarily be linear. If the polynomial trend line (Figure 4b) was chosen, an increase in the CD curve was observed up to a certain wheat consumption level (approximately 75-80 kg per capita per year), and then the CD values showed a tendency to decrease. It remains unclear whether this was a real trend or a false CD decline due to a lack of data and scattering of available data.

We found a non-significant correlation ($r = -0.036$, $p > 0.50$) when the data were compared by country (Figure 5). The country-wide reliable correlation between wheat consumption and the prevalence of biopsy proved CD could not be obtained because the data were dissipated, and statistical relationships were unreliable ($p > 0.5$). The significant differences between the data may be due to the fact mentioned above that, in some countries, only the prevalence of CD among children has been studied, which can be 2-5-fold higher than in adults (Ashtari et al. 2021; Mariné et al. 2011). CD prevalence data based on different age groups may have contributed to the inaccuracy of the results. We also obtained a trend of nonlinear correlation. The prevalence of CD was directly dependent on gluten intake only in small amounts (up to 78 kg per year) ($r = 0.80$, $p < 0.05$). This dependence was observed in other studies (Catassi et al. 1993; Lionetti and Catassi 2014), and our results confirmed this. On the other hand, as this dependence is strong when analyzing pooled data by continent, it is not yet clear whether the dependence disappears with increasing wheat consumption, whether it is not possible to determine, or whether rising wheat consumption in countries actually reduces the risk of CD. Although this intention is observed in most countries, the low correlation and statistical uncertainty are due to a lack of reliable data on the prevalence of CD in countries with the highest wheat consumption.

The lack of correlation may also have been influenced by other factors. The large difference in the prevalence of CD among European countries remains unclear. Thus, although European countries have similar living conditions, they share a similar distribution of causal factors (level of gluten intake and frequency of HLA-DQ haplotype), and the incidence of CD varies widely. The reasons for these differences could be due to other factors (infant feeding patterns, spectrum of intestinal infections, human intestinal microbiome, *etc.*, which we have discussed above. Biopsy-proven CD was 2-6-fold more common in Sweden than in neighboring countries such as Finland and Denmark, even though a similar rate of sero-prevalence among blood donors in both countries was found in a previous study (Weile et al. 2001). We agree with the speculation of Kang et al. (2013), who found that the difference may be more obvious than true due to varying indices of suspicion. Another possible explanation is that it may be linked to significantly different socioeconomic conditions, resulting in differences in gut microflora, the frequency of intestinal infections, and a variety of dietary factors other than gluten (Kondrashova et al. 2008).

Previous research on the correlation between wheat consumption and CD prevalence performed by Lionetti and Catassi (2014) showed no significant correlation between the level of wheat consumption and the nationwide prevalence of CD; however, they found that the prevalence of CD is influenced by the history of wheat consumption. Some studies (Yuan et al. 2017; Zhou et al. 2020) have also shown that rapidly increasing gluten consumption in some countries has led to a sharp rise in the prevalence of CD. Therefore, we investigated whether the incidence of CD was affected by the dynamics of wheat consumption. We examined whether there is a direct relationship between the relative increase/decrease in wheat consumption in the long and short term and CD. Statistical analysis showed a small direct dependence of CD prevalence on short-term wheat consumption variation, and a negative correlation with an increase/

decrease in long-term wheat consumption, but the data were unreliable ($p > 0.5$). Thus, it can be stated that the prevalence of CD was influenced more by the consumption of wheat than by changes in its consumption over the last few decades.

Limitations of our study

The lack of reliable studies on the prevalence of CD in different countries. The screening results of healthy blood donors and children may not fully reflect the disease situation in the general population. Not all individuals who were invited to undergo a biopsy after a serological test agreed to participate. FAO wheat consumption data do not take into account the difference in wheat consumption between individual regions of large countries, unconsumed leftovers, and individual wheat intake. In assessing the relationship between wheat consumption and CD by continent, the fact that the overall average wheat consumption in Africa is low, but data on CD were found in African countries with high wheat consumption is worrying.

We also did not estimate the increasing vital gluten intake; we did not analyze the effect of new wheat varieties with high gluten content on CD prevalence.

Thus, although we have shown that there is a strong relationship between wheat intake and the prevalence of CD, many questions remain unanswered. There is a need for well-designed, population-based CD prevalence studies from many parts of the world to assess this relationship and use it to predict CD cases in countries with a scarcity of diagnostic facilities.

Conclusions

The prevalence of biopsy-proven global CD was estimated 0.77%. The highest prevalence of CD (1.07%) has been observed in Europe, as compared with other continents. The high positive correlation ($r = 0.88$, $p < 0.05$) between wheat consumption and the prevalence of CD (biopsy-proved) was established by estimating data by continent; however a non-significant correlation was found ($r = -0.036$; $p > 0.50$) when the data were compared by country. A trend of direct relationship with prevalence of CD was observed only in countries with low wheat consumption (up to 78 kg per year). Changes in wheat consumption in the last few decades have no significant effects on the development of CD assessed either by country or by continent.

Disclosure statement

Carlo Catassi is a scientific consultant to Schär Food, Takeda, and NOOS, Italy. No other potential conflict of interest waa reported by other authors.

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