Incidence of Celiac Disease Is Increasing Over Time: A Systematic Review and Meta-analysis

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OBJECTIVES: **To conduct a systematic review and meta-analysis that defines the worldwide incidence of celiac disease (CD) and examines temporal trends.**

METHODS: **MEDLINE and EMBASE were searched for population-based studies reporting the incidence of CD in the overall population, children, or adults. No limits were placed on year or language of publication. Studies solely examining at-risk populations (e.g., patients with type 1 diabetes) were excluded. Random-effects models were performed to meta-analyze sex- and age-specific incidence in the 21st century. Temporal trend analyses assessed the average annual percent change in CD incidence over time.**

RESULTS: **Of 11,189 citations, 86 eligible studies were identified for inclusion, of which 50 were deemed suitable for analyses. In the 21st century, the pooled female incidence of CD was 17.4 (95% confidence interval [CI]: 13.7, 21.1) (I^2 = 99.5%) per 100,000 person-years, compared with 7.8 (95% CI: 6.3, 9.2) (I^2 = 98.6%) in males. Child-specific incidence was 21.3 per 100,000 person-years (95% CI: 15.9, 26.7) (I^2 = 99.7%) compared with 12.9 (95% CI: 7.6, 18.2) (I^2 = 99.9%) in adults. Pooling average annual percent changes showed the incidence of CD to be increasing by 7.5% (95% CI: 5.8, 9.3) (I^2 = 79.6%) per year over the past several decades.**

DISCUSSION: **Incidence of CD is highest in females and children. Overall, the incidence has been significantly rising in the latter half of the 20th century and into the 21st century throughout the Western world. Population-based studies in Africa, Asia, and Latin America are needed to provide a comprehensive picture of the global incidence of CD.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B367, http://links.lww.com/AJG/B368, http://links.lww.com/AJG/B369, http://links.lww.com/AJG/B370, http://links.lww.com/AJG/B371, http://links.lww.com/AJG/B372, http://links.lww.com/AJG/B373, http://links.lww.com/AJG/B374, http://links.lww.com/AJG/B375, http://links.lww.com/AJG/B376

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BACKGROUND

Celiac disease (CD) is an immune-mediated condition characterized by small intestinal inflammation from gluten ingestion. The prevalence of biopsy-confirmed CD is estimated at 0.7%, while diagnosis based on serology is estimated at 1.4% of the population (1). The incidence of CD varies geographically and appears to be increasing over time in several regions of the world (2,3). Screening studies suggest that CD is underdiagnosed, likely due to individuals presenting with nonclassical or silent CD (4,5).

CD is associated with significant burdens to patients and society including elevated financial costs of a gluten-free diet (6–8), inadvertent exposure to gluten (9,10), psychosocial impacts of adhering to a strict diet (11,12), and increased risk of complications (13). Therefore, it is essential to have a comprehensive understanding of CD epidemiology throughout the world to ensure healthcare systems are adequately prepared for the potential burden, as well as to identify new clues in the pathogenesis of the condition.

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We performed a systematic review and meta-analysis of population-based studies reporting the incidence of CD, analyzed temporal trends of incidence, and explored differences by age and sex.

METHODS

Search strategy and study selection

This systematic review is registered in PROSPERO (ID: CRD42018084112), the International prospective register of systematic reviews (https://www.crd.york.ac.uk/PROSPERO). We conducted our systematic review in accordance with the meta-analysis of observational studies in epidemiology (14). Our search was designed to identify population-based studies reporting the incidence of diagnosed CD. With consultation of a research librarian, we performed a systematic literature search of MEDLINE and EMBASE up to September 25, 2019. We did not place any restrictions on language. Our search terms are provided in Supplementary Digital Content 1 (see Table S1, http://links.lww.com/AJG/B367).

Citations were independently reviewed in duplicate (J.A.K., J.J., and F.E.U.), and disagreements were resolved through discussion (G.G.K.). Full-texts were independently assessed in duplicate and excluded if they were not a full article (e.g., letter), an original study (e.g., literature review), population-based, reported incidence in a specific population (e.g., patients with diabetes), or contained potential data errors unverified by corresponding authors. Non-English texts were translated using Google Translate (translate.google.com). Reference lists of previous systematic reviews (2,3), review articles, and included studies were examined to identify other articles not captured in our database search.

Data extraction

When available, the following data were extracted in duplicate from included studies: first author and year of publication, geographic information, period, diagnostic criteria and case ascertainment used to define CD, number of cases diagnosed, and overall, age-specific, sex-specific, and/or annual incidence. A detailed description of the methods used for calculations is summarized in Supplementary Digital Content 2 (see Table S2, http://links.lww.com/AJG/B368). Where numerical values for incidence were represented within a graph, incidence values were estimated using OriginPro 2018 (originlab.com). Corresponding authors of included studies were contacted to obtain additional data not presented in the article. If more than 1 study reported incidence in the same geographic area and period, data from the most recently published study were used. Age-specific incidence rates reported in this review represent approximations of children (e.g., <15 years) and adults (e.g., >18 years), depending on study definition.

Data analysis and quality assessment

Analysis was limited to studies reporting incidence per person-years and published as full-texts. Articles that reported cumulative incidence per live births are summarized in Supplementary Digital Content 3 (see Table S3, http://links.lww.com/AJG/B369) but were not included in the analysis due to an inability to make meaningful comparisons with more recent data. Quality assessment of the included studies, performed independently in duplicate, was based on an adapted version of the Newcastle-Ottawa Assessment Scale (15), using criteria specifically relevant to population-based studies of incidence.

Studies that provided incidence rates for at least 5 years (i.e., 5 or more data points) were investigated for temporal trend analysis. Joinpoint regression models were used to calculate the average annual percent change (AAPC) in incidence trends (surveillance.cancer.gov/joinpoint/). This analysis assumes the dependent variable counts follow a Poisson distribution (and variance), using the year as the predictor variable. We also assessed for inflection points within these temporal trends (1 inflection point tested per 10 data points). Studies providing temporal data were used to create scatter plots demonstrating changes in CD incidence over time.

Two choropleth maps were created using QGIS 2.18 (www.osgeo.org) to demonstrate geographic differences in incidence before and after the turn of the century. Shades of colors to represent varying levels of incidence were determined through terciles based on the overall incidence value from each study (see Supplementary Digital Content 2, Table S2, http://links.lww.com/AJG/B368 for the methods used to divide countries into terciles: <4.6, 4.6–12.7, >12.7 per 100,000 person-years). An interactive web-based map was created using ArcGIS Pro 2.3.0 and ArcGIS Online (www.esri.com/en-us/home).

Random-effects models were used to pool sex- and age-specific incidence values and associated 95% confidence intervals (CIs) from data in the 21st century (www.stata.com). Studies that provided sex-specific data for all ages were used to calculate the pooled sex-specific rates. Studies providing child and/or adult-specific data were used to calculate the pooled age-specific rates. We also pooled incidence rate ratios (IRRs) by sex and age, respectively, and performed sub-group analyses to explore whether the sex differences in CD incidence differed by age category. We also performed meta-analyses on the AAPCs. Studies with multiple periods in the same geographic region were analyzed for 1 overall AAPC. Estimates which covered the largest geographic region and/or the most recent period was included in all meta-analyses to minimize overlapping data. For all meta-analyses, statistical heterogeneity was assessed using the I^2 statistic.

RESULTS

Our search strategy yielded 11,189 unique citations with 461 eligible for full-text review (Figure 1). In total, 86 studies met our inclusion criteria, but 36 studies were not analyzed because they reported incidence per live births (see Supplementary Digital Content 3, Table S3, http://links.lww.com/AJG/B369). The 50 studies with data suitable for analysis were based in Europe (n = 42), North America (n = 7), and Oceania (n = 1) (16–65). The incidence of CD among all ages was reported in 21 studies (Table 1). Nineteen studies focused exclusively on children for a total of 29 studies reporting on overall incidence in children (Table 2); nine studies focused solely on adults for a total of 19 studies reporting on overall incidence in adults (Table 3).

Incidence of CD

Incidence (per 100,000 person-years) from included studies is summarized in Tables 1–3. Choropleth maps illustrate geographic differences in the incidence of CD before and after 2000 (Figure 2), and an interactive web-based map is available at this link: https://wpsites.ucalgary.ca/gilkaplan/global-celiac-disease-incidence/.

In the 21st century, the pooled incidence of CD among females was 17.4 (95% CI: 13.7, 21.1) per 100,000 person-years (n = 7) (Figure 3a), compared with 7.8 (95% CI: 6.3, 9.2) among males (n = 7) (Figure 3b). These meta-analyses revealed high

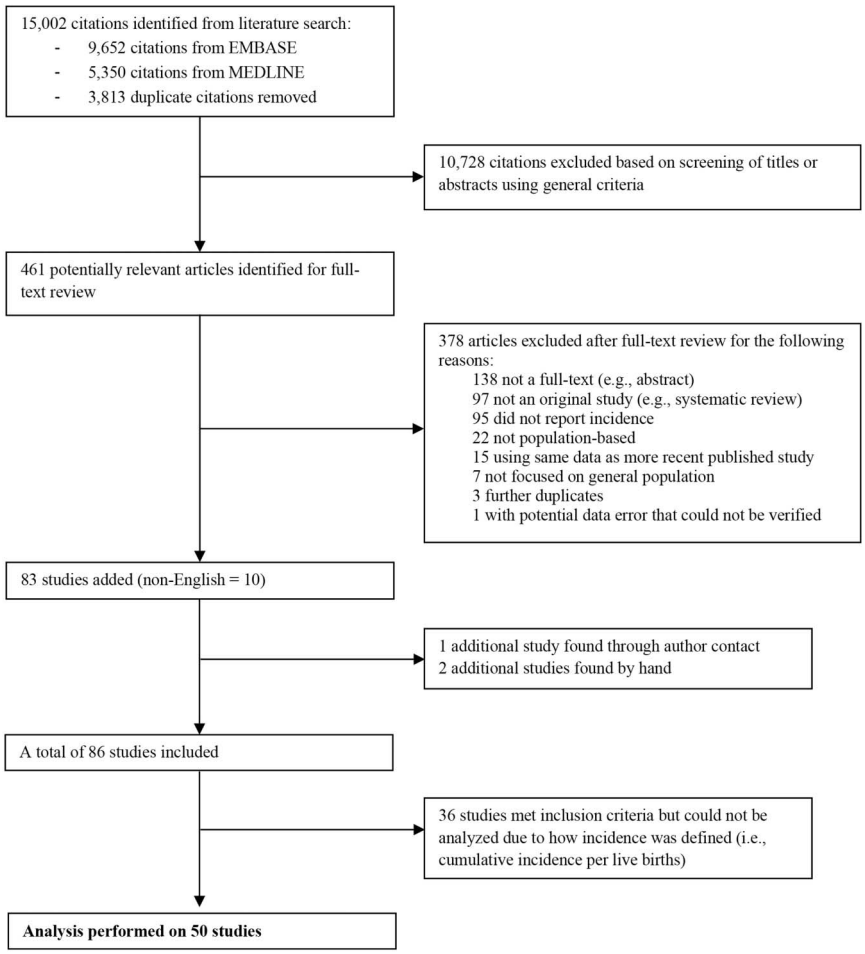

Figure 1. Flow chart outlining inclusion procedure.

heterogeneity, with I^2 values of 99.5% and 98.6%, respectively. The pooled female-to-male IRR was 2.1 overall (95% CI: 1.9, 2.3) (n = 7) (I^2 = 80.0%), 1.8 in children only (95% CI: 1.7, 1.9) (n = 5) (I^2 = 11.8%), and 1.8 in adults only (95% CI: 1.5, 2.1) (n = 4) (I^2 = 95.8%) (see Supplementary Digital Content 4, Figures S1–2, http://links.lww.com/AJG/B370 for respective forest plots).

The pooled incidence of pediatric CD in the 21st century was 21.3 (95% CI: 15.9, 26.7) per 100,000 person-years (n = 15) (Figure 4a) compared with 12.9 (95% CI: 7.6, 18.2) in adults (n = 10) (Figure 4b). High heterogeneity was present in these meta-analyses, with I^2 values of 99.7% an 99.9%, respectively. The pooled child-to-adult IRR was 1.7 (95% CI: 1.2, 2.3) (n = 6) (I^2 = 98.4%) (see Supplementary Digital Content 5, Figure S3, Table S4, http://links.lww.com/AJG/B371 for forest plot and sensitivity analysis of age-specific estimates).

Temporal analyses showed 72.7% of studies (24 of 33) had statistically significant increasing incidence over time (see Supplementary Digital Content 6, Table S5, http://links.lww.com/AJG/B372). Figure 5 is a scatter plot demonstrating temporal changes in the overall incidence of CD (see Supplementary Digital Content 7, Figure S4, http://links.lww.com/AJG/B373 for child- and adult-specific scatter plots). Pooling all AAPCs showed the incidence of CD to be increasing at 7.5% (95% CI: 5.8, 9.3) (n = 18) (I^2 = 79.6%) per year over the past several decades (see Supplementary Digital Content 8, Figure S5, http://links.lww.com/AJG/B374 for forest plot). Sensitivity analyses show this trend to be consistent across geographic, sex, and age categories, (see Supplementary Digital Content 9, Table S6, http://links.lww.com/AJG/B375).

The incidence of CD has been increasing over time in most regions. For example, incidence of CD in Olmsted County, USA, increased on average by 8.1% (95% CI: 4.6, 11.7) per year from 1950 to 2010 (33,34); pediatric incidence in Southeast Scotland, United Kingdom, increased by 12.8% (95% CI: 11.4, 14.1) per year from 1990 to 2016 (42,45); and adult incidence in Cardiff and Vale of Glamorgan, Wales, United Kingdom, increased by 11.3% (95% CI: 9.3, 13.4) from 1981 to 2005 (19,20). However, some regions exhibited inflection points whereby the slope of the AAPC changed over time. For example, Sweden saw a rapid rise in pediatric incidence from 1998 to 2003 (AAPC = 21.9%; 95% CI: 5.9, 40.3), until stabilizing from 2003 to 2009 (AAPC = −3.1%; 95% CI: −9.2, 3.4) (40).

Other countries demonstrated stabilizing rates in recent periods. Among children, incidence rates in Tampere, Finland, were stable after an inflection point in 2007 (annual percent change = −3.0%; 95% CI: −9.1, 3.6) (37); in South Wales, United Kingdom, incidence was stable from 2005 to 2011 (annual percent change = 5.8%; 95% CI: −2.9, 15.3) (43). The only country with decreasing incidence was among adults in Finland, from 2005 to 2014 (AAPC = −3.4%; 95% CI: −4.6, −2.2) (59).

Table 1. Incidence of CD per 100,000 person-years (all ages)

Study	Country (area)	Case ascertainment	Diagnostic criteria	Period	New cases	Incidence (per 100,000)
Northern Europe						
Grode et al. (16)[a]	Denmark (Nationwide)	Danish National Patient Register: Primary or secondary diagnosis of CD using *ICD-8* codes 269.00, 269.98 and *ICD-10* code K90.0	Used gastroscopy procedure as proxy measure for biopsy	1980–2016	11,550	5.9
Sher et al. (17)	United Kingdom (Leicestershire, England)	1) Leicester hospital records 2) Questionnaires to general practitioners 3) The Coeliac Society	*Children*: ESPGAN criteria (1970, 1990) *Adults*: Cluysenaer and van Tongren criteria	1975–1989	106	2.5[b]
Fowell et al. (18)	United Kingdom (East Dorset, England)	Poole Hospital records	Biopsy-proven	1993–2002	159	8.7
Stroud et al. (64)	United Kingdom (Southern England)	1) Endoscopy and histopathology records 2) Gastroenterology and pediatric clinics 3) Dedicated celiac clinic	Biopsy-proven, ESPGHAN criteria (2012) for children 2012 onward	1993–2017	802	12.8[b]
Hawkes et al. (19)[a]	United Kingdom (Cardiff and Vale of Glamorgan, Wales)	1) Cardiff teaching hospital records 2) Hospital activity data 3) Questionnaires to general practitioners/hospital consultants 4) Questionnaire to the Coeliac Society	ESPGAN criteria (1990)	1981–1995	137	2.2[b]
Hurley et al. (20)[a]	United Kingdom (Cardiff and Vale of Glamorgan, Wales)	1) Cardiff and the Vale of Glamorgan hospital records 2) Letters to National Health Service and private hospitals practitioners/hospital consultants 3) Hospitals outside area contacted to identify patients in geographic boundaries	ESPGHAN criteria (1990)	1996–2005	347	8.1[b]
West et al. (21)	United Kingdom (Nationwide)	Clinical Practice Research Datalink: Read codes J690.00, J690.13, J690z00, J690100, J690.14, J690000	Not stated	1990–2011	9,087	13.8
	England	Clinical Practice Research Datalink: Read codes J690.00, J690.13, J690z00, J690100, J690.14, J690000	Not stated	1990–2011	6,946	13.2[b]
	Northern Ireland	Clinical Practice Research Datalink: Read codes J690.00, J690.13, J690z00, J690100, J690.14, J690000	Not stated	1990–2011	510	22.3
	Scotland	Clinical Practice Research Datalink: Read codes J690.00, J690.13, J690z00, J690100, J690.14, J690000	Not stated	1990–2011	887	16.9

Table 1. (*continued*)

Study	Country (area)	Case ascertainment	Diagnostic criteria	Period	New cases	Incidence (per 100,000)
	Wales	Clinical Practice Research Datalink: Read codes J690.00, J690.13, J690z00, J690100, J690.14, J690000	Not stated	1990–2011	744	13.1
West et al. (65)	United Kingdom (Nationwide)	Clinical Practice Research Datalink: Read codes J690.00, J690.13, J690z00, J690100, J690.14, J690000 (follow-up study to West at al. (21))	Not stated	2005–2015	8,177	18.0
Southern Europe						
Corrao et al. (22)	Italy (Piedmont/ Lombardia/Umbria/ Sardinia)	1) Hospital records in study areas and leading Italian hospitals 2) National records of patients provided gluten-free foods 3) Archives of Italian Coeliac Society	Biopsy-proven by single histology finding or ESPGAN criteria (1970)	1990–1991	270	2.1
Lanzarotto et al. (23)	Italy (Brescia)	Hospital records from provincial network in Brescia	Marsh criteria (1992)	1996–1997	135	6.6[b]
Lanzini et al. (24)	Italy (Brescia)	Hospital records from provincial network in Brescia	Modified Marsh criteria (1999)	2001–2003	508	17.0
Angeli et al. (25)	Italy (Terni)	Terni Province Health Board No 4: Individuals with prescription for specific medical treatment	Not stated[c]	2002–2010	330	16.3[b]
Zingone et al. (26)	Italy (Campania)	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)[d]	2011–2013	2,049	11.8
	Avellino	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)[d]	2011–2013	156	12.0
	Benevento	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)[d]	2011–2013	57	6.6
	Caserta	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)[d]	2011–2013	281	10.3
	Naples	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)[d]	2011–2013	1,082	11.8
	Salerno	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)[d]	2011–2013	473	14.3
Western Europe						
Gutschmidt et al. (27)	Germany (West Berlin)	Records of local Pathological Institutes	Abnormal specimens typical of CD	1979–1984	83	0.7

Table 1. (*continued*)

Study	Country (area)	Case ascertainment	Diagnostic criteria	Period	New cases	Incidence (per 100,000)
Jansen et al. (28)	Netherlands (Nationwide)	Registered members of the Dutch Coeliac Disease Society	Biopsy-proven	1975–1991	1,622	0.6[b]
Burger et al. (29)	Netherlands (Nationwide)	Dutch Pathology Registry	Marsh criteria (1992)	1995–2010[e]	4,014	5.0[b]
Oceania						
Ussher et al. (30)	New Zealand (Wellington)	Hospital records in Kapiti Coast, Porirua City, Wellington City, Masterton District, Carterton District, and South Wairarapa	Malabsorption, abnormal histology, and clinical response to gluten-free diet	1985–1992	38	1.8
Cook et al. (31)	New Zealand (Canterbury)	Database with new diagnoses registered from gastroenterology and pediatric departments in Canterbury	Marsh type 3 lesion	1970–1999	416	3.7[b]
Northern America						
Stewart et al. (32)	Canada (Calgary)	Pathology and endoscopy databases	Modified Marsh criteria (1999)	2004–2008	763	12.8[b]
Murray et al. (33)	United States (Olmsted County)	1) Rochester Epidemiology Project 2) CD support group membership 3) Records of Mayo Department of Pathology and Laboratory Medicine	ESPGAN criteria (1990)	1950–2001	82	2.1
Ludvigsson et al. (34)	United States (Olmsted County)	1) Rochester Epidemiology Project 2) Electronic medical records (Mayo Clinic Life Sciences System) 3) Patient charts with *ICD-9* code 579.0	Not stated	2000–2010	249	17.4

CD, celiac disease; ESPGAN, The European Society for Paediatric Gastroenterology and Nutrition; ESPGHAN, The European Society for Paediatric Gastroenterology Hepatology and Nutrition; ICD, International Classification of Diseases.
[a]Additional data provided by authors.
[b]Overall incidence calculated (see Supplementary Digital Content 2, Table S2, http://links.lww.com/AJG/B368 for formula).
[c]To receive exemption, patients require histological confirmation of disease.
[d]In the absence of biopsy confirmation, justification for diagnosis provided.
[e]Represents years 1995, 2000, 2005, 2008, and 2010.

Quality assessment for each study is provided in Supplementary Digital Content 10 (see Table S7, http://links.lww.com/AJG/B376). Overall, risk of bias in included studies was low. Although there was variation in the criteria used to define and measure CD, most studies based the diagnosis on the gold standard of biopsy confirmation. In addition, most studies used registries, hospital records, or CD-specific databases—with these types of data sources, authors were able to collect information on the date of diagnosis, thereby reducing the risk of misclassifying prevalent cases as incident. In terms of temporal analyses among studies that were assessed for quality, 17 were able to assess for at least 1 inflection point, whereas 12 could only estimate an overall AAPC.

DISCUSSION

Over the past few decades, the incidence of CD has dramatically increased in many industrialized nations, contributing to an increasing burden on society and healthcare systems. Once regarded as a condition manifesting predominantly in childhood, CD has emerged as a common diagnosis in adults. CD continues to be disproportionately diagnosed in females, although incidence is still increasing among males. The incidence of CD has been widely studied throughout Europe, North America, and Oceania. By contrast, population-based studies on the incidence of CD are lacking from Africa, Asia, and Latin America. Future epidemiological studies are needed in these areas to comprehensively evaluate the global epidemiology of CD.

The introduction of noninvasive and accurate serological testing for CD near the end of the 20th century made diagnosing CD more efficient and cost-effective (66,67). For example, in Calgary, Canada, the incidence of pediatric CD tripled after the implementation of antiendomysial antibody testing (50). Diagnostic guidelines for CD have also shifted over time, leading to increased diagnoses (68–70). For example, European Society for Paediatric Gastroenterology Hepatology and Nutrition guidelines now allow serological diagnoses of CD without biopsy confirmation in children who meet certain clinical, genetic, and serologic criteria (71). As observed in Southeast Scotland, United

Table 2. Incidence of CD per 100,000 person-years (children)

Study	Country (area)	Case ascertainment	Diagnostic criteria	Period	New cases	Incidence (per 100,000)
Northern Europe						
Dydensborg et al. (35)[a]	Denmark (Nationwide)	1) Danish National Patient Registry (ICD-10 coding) 2) National Registry of Pathology 3) Hospital records	Modified Marsh criteria (1999)	1996–2009	1,188	7.1[b,c]
Grode et al. (16)[a]	Denmark (Nationwide)	Danish National Patient Register: Primary or secondary diagnosis of CD using *ICD-8* codes 269.00, 269.98 and *ICD-10* code K90.0	Utilized gastroscopy procedure as proxy measure for biopsy	1980–2016	4,121	8.5[b]
Ress et al. (36)	Estonia (Nationwide)	1) Contact to district pediatricians and hospital records (1976–1989) 2) Records from Children's Clinic of Tartu University Hospital and Tallinn Children's Hospital (1990–2010)	ESPGAN criteria (1990)	1976–2010	152	1.1
Kivela et al. (37)	Finland (Tampere)	1) Research database following children with CD 2) Medical records	Elevated TG2ab/EmA	2001–2013	—	44.0[b]
Perminow et al. (38)	Norway (Akershus)	Hospital records from Akershus Central Hospital	Biopsy-proven	1993–1998	—	16.9[d]
Beitnes et al. (39)	Norway (Southeast)	Hospital records from Akershus University Hospital, Oslo University Hospital Ullevål, and Østfold Hospital Trust (SØ)	Marsh type 2 or 3 lesion	2000–2010[e]	400	31.4[b]
Namatovu et al. (40)	Sweden (Nationwide)	1) National Swedish Childhood CD Register (1991–2009) 2) Records from 5 pediatric units (1973–1990) retrospectively added to register	ESPGAN criteria (1970, 1990)	1973–2009[f]	9,107	25.9[b]
Tapsas et al. (41)	Sweden (Östergötland)	Regional CD register	ESPGAN criteria (1990)[g]	1973–2013	1,030	28.2[b]
Sher et al. (17)	United Kingdom (Leicestershire, England)	1) Leicester hospital records 2) Questionnaires to general practitioners 3) The Coeliac Society	ESPGAN criteria (1970, 1990)	1975–1989	24	2.8[b]
Fowell et al. (18)	United Kingdom (East Dorset, England)	Poole Hospital records	Biopsy-proven	1993–2002	—	2.5
Hawkes et al. (19)[a]	United Kingdom (Cardiff and Vale of Glamorgan, Wales)	1) Cardiff teaching hospital records 2) Hospital activity data 3) Questionnaires to general practitioners/hospital consultants 4) Questionnaire to the Coeliac Society	ESPGAN criteria (1990)	1981–1995	27	2.3[b]

Table 2. (*continued*)

Study	Country (area)	Case ascertainment	Diagnostic criteria	Period	New cases	Incidence (per 100,000)
Hurley et al. (20)[a]	United Kingdom (Cardiff and Vale of Glamorgan, Wales)	1) Cardiff and the Vale of Glamorgan hospital records 2) Letters to National Health Service and private hospitals practitioners/hospital consultants 3) Hospitals outside area contacted to identify patients in geographic boundaries	ESPGHAN criteria (1990)	1996–2005	42	5.0[b]
White et al. (42)[a]	United Kingdom (Southeast Scotland, Scotland)	1) Hospital records (*ICD-10* coding) 2) Pathology records 3) Clinical database 4) Serology database 5) Electronic hospital records	ESPGHAN criteria (1990)	1990–2009	266	5.6[b]
West et al. (21)	United Kingdom (Nationwide)	Clinical Practice Research Datalink: Read codes J690.00, J690.13, J690z00, J690100, J690.14, J690000	Not stated	1990–2011	1,319	10.4
Whyte and Jenkins (43)	United Kingdom (South Wales, Wales)	1) Regional Paediatric Gastroenterology Centre 2) CD Database 3) Histopathology/Regional Immunology Database 4) Dietetic Records	ESPGHAN criteria (1990)	2005–2011	163	8.2[b]
Zingone et al. (44)	United Kingdom (Nationwide)	The Health Improvement Network: Read codes J690.00, J690.13, J690z00.	Not stated	1993–2012	1,247	11.9[b]
	England	The Health Improvement Network: Read codes J690.00, J690.13, J690z00.	Not stated	1993–2012	1,003	12.2
	Northern Ireland	The Health Improvement Network: Read codes J690.00, J690.13, J690z00.	Not stated	1993–2012	139	10.8
	Scotland	The Health Improvement Network: Read codes J690.00, J690.13, J690z00.	Not stated	1993–2012	69	10.6
	Wales	The Health Improvement Network: Read codes J690.00, J690.13, J690z00.	Not stated	1993–2012	36	9.5
Lister et al. (45)	United Kingdom (Southeast Scotland, Scotland)	Follow-up data from White et al. (42)	ESPGHAN criteria (2012)	2010–2016	382	23.9
Southern Europe						
Zingone et al. (26)	Italy (Campania)	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)	2011–2013	1,059	27.4[b]

Table 2. (*continued*)

Study	Country (area)	Case ascertainment	Diagnostic criteria	Period	New cases	Incidence (per 100,000)
	Avellino	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)	2011–2013	68	27.4[b]
	Benevento	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)	2011–2013	31	18.9[b]
	Caserta	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)	2011–2013	128	20.4[b]
	Naples	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)	2011–2013	602	27.9[b]
	Salerno	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)	2011–2013	230	34.5[b]
Lopez-Rodriguez et al. (46)	Spain (Caceres)	Hospital records from San Pedro de Alcántara Hospital	ESPGHAN criteria (1990)	1981–1999	157	10.6[b]
Cilleruelo et al. (47)	Spain (Nationwide)[h]	Pediatric gastroenterology units contacted through the Spanish Society of Pediatric Gastroenterology, Hepatology, and Nutrition	ESPGHAN criteria (1990)	2006–2007	659	54.0
Eastern Europe						
Vukavic (48)	Serbia (Voyvodina)[i]	Contacting pediatricians in the region	ESPGHAN criteria (1970)	1980–1993	201	3.5
Western Europe						
Burger et al. (29)	Netherlands (Nationwide)	Dutch Pathology Registry	Marsh criteria (1992)	1995–2010[j]	1,431	8.2[b]
Van Kalleveen et al. (49)	Netherlands (Blaricum)	Hospital records from Tergooi Hospital	ESPGHAN criteria (1990/2012) for 2007–2011/2012–2016	2007–2016	105	21.1
Oceania						
Cook et al. (31)	New Zealand	Database with new diagnoses registered from gastroenterology and pediatric departments in Canterbury	Marsh type 3 lesion	1970–1999	84	2.3

Table 2. (*continued*)

Study	Country (area)	Case ascertainment	Diagnostic criteria	Period	New cases	Incidence (per 100,000)
Northern America						
McGowan et al. (50)[a]	Canada (Calgary)	1) Calgary Laboratory Services pathology database 2) Clinic records from Alberta Children's Hospital	NASPGHAN criteria (2005)	1990–2006[k]	235	5.2[b]
Rajani et al. (51)	Canada (Northern Alberta)	1) Clinical charts at Stollery Children's Hospital 2) Division of Pediatric Gastroenterology and Nutrition database	Marsh criteria (1992)	1998–2007	158	6.5[b]
Stewart et al. (52)	Canada (Calgary)	Pathology and endoscopy databases	Modified Marsh criteria (1999)	2004–2008	245	16.6[b]
Almallouhi et al. (53)	United States (Olmsted County)	1) Rochester Epidemiology Project for *ICD-9* code 579.0 2) Screening databases used in previous studies 3) Records from Mayo Clinic and Olmsted Medical Center	NASPGHAN criteria (2005), ESPGHAN criteria (2012)	2000–2014	100	17.4

CD, celiac disease; ESPGAN, The European Society for Paediatric Gastroenterology and Nutrition; ESPGHAN, The European Society for Paediatric Gastroenterology Hepatology and Nutrition; ICD, International Classification of Diseases; NASPGHAN, North American Society For Pediatric Gastroenterology, Hepatology and Nutrition.
[a]Additional data provided by authors.
[b]Overall incidence calculated (see Supplementary Digital Content 2, Table S2, http://links.lww.com/AJG/B368 for formula).
[c]Incidence for verified diagnosis from National Registry of Pathology was 0.8 (1996), 1.4 (1999), and 6.9 (2009).
[d]Data retrieved from Beitnes et al. (39).
[e]Represents periods 2000–2002 and 2008–2010.
[f]Olsson et al. (62) overlapped with this time period and geographic region; therefore data not shown.
[g]Forty-three patients diagnosed with ESPGHAN criteria (2012).
[h]Incidence value calculated based on 24 of 39 participating centers.
[i]Study performed when region was part of Yugoslavia.
[j]Represents years 1995, 2000, 2005, 2008, and 2010.
[k]Represents periods 1990–1996 and 2000–2006.

Kingdom, 56% of children in 2016 were diagnosed without biopsy (45). Simplified testing has also led to increased referrals to gastroenterologists for endoscopy, particularly for patients with milder gastrointestinal symptoms (72).

Increased recognition of CD by physicians has led to evaluating patients with "nonclassical" presentations (i.e., extraintestinal symptoms) (73). Screening strategies have also been adopted to identify CD in asymptomatic individuals belonging to groups potentially at-risk such as those with type 1 diabetes, autism, or first-degree relatives with CD (74–76). This may be reflected in the significant increase of celiac-specific serologies requested in healthcare settings (77,78). Moreover, the gluten-free diet has become ubiquitous within society leading patients to advocate to their primary care physicians for CD testing (79).

Screening studies among adults show similar occurrence of CD in men and women (80–82). Thus, the reasons for CD diagnoses being approximately twice as common in females may be related to sex-differences in healthcare utilization patterns. As some comorbid conditions associated with CD are more commonly diagnosed in women (e.g., hypothyroidism), these initial diagnoses may lead to a higher rate of detection of CD among females (83). As incidence increased over time, this sex difference seems to have amplified in some countries (16,29,44,53). These trends should be further evaluated to identify genuine sex differences and/or underdiagnosis in males.

The definition of CD represented in studies refers to diagnosed cases, and thus, the incidence reported is an underestimation of the true number of individuals who develop CD in the population. With greater awareness of CD, the incidence of diagnosed CD will begin to approach the true incidence in the population. In our pooled analyses, children were 2 times more likely to be diagnosed with CD compared to adults. However, several epidemiologic patterns show the average age at diagnosis among children to be rising (36,37,41,42,46,50). Furthermore, the age-specific differences in incidence of CD varied by region as studies from New Zealand, United Kingdom, and the United States demonstrated adult incidence to be higher than pediatric incidence (21,31,33,34). The rising incidence and the shifting demographics of CD is in part explained by better recognition and screening in adults.

Importantly, a genuine increase in CD incidence is occurring beyond diagnostic improvements, most likely due to environmental factors (80,84,85). The "Swedish Epidemic" of CD represents interesting patterns in pediatric incidence and has been a major source for investigating possible causal mechanisms

Table 3. Incidence of CD per 100,000 person-years (adults)

Study	Country (area)	Case ascertainment	Diagnostic criteria	Period	New cases	Incidence (per 100,000)
Northern Europe						
Bode and Gudmand-Hoyer (54)	Denmark (Copenhagen)	1) Hospital discharges with *ICD* code 269.0 or 269.01 2) Pathology records at university hospitals 3) Case register of CD patients	ESPGAN criteria (1990)	1976–1991	101	1.3
Schosler et al. (55)	Denmark (Aarhus County)	1) National Danish Discharge Registry: *ICD-10* code DK90.0	ACG guidelines (2013)	2008–2013	93	6.3[b]
Grode et al. (16)[a]	Denmark (nationwide)	Danish National Patient Register: primary or secondary diagnosis of CD using *ICD-8* codes 269.00, 269.98 and *ICD-10* code K90.0	Utilized gastroscopy procedure as proxy measure for biopsy	1980–2016	7,429	5.0[b]
Collin et al. (56)	Finland (Tampere)	Records from the University Hospital, City Hospital, and the Local Health Center	Biopsy-proven and response to gluten-free diet	1975–1994	368	9.7[b]
Collin et al. (57)	Finland (nationwide)	Epidemiologic survey based on physician statements	Biopsy-proven[c]	1980–2003	—	15.6[b]
Virta et al. (58)	Finland (nationwide)	Dietary grants in the Social Insurance Institution using *ICD* code K90	Mucosal villous atrophy	2004–2006	5,020	39.3
	Helsinki	Dietary grants in the Social Insurance Institution using *ICD* code K90	Mucosal villous atrophy	2004–2006	1,387	32.4
	Kuopio	Dietary grants in the Social Insurance Institution using *ICD* code K90	Mucosal villous atrophy	2004–2006	806	38.3
	Oulu	Dietary grants in the Social Insurance Institution using *ICD* code K90	Mucosal villous atrophy	2004–2006	836	48.5
	Tampere	Dietary grants in the Social Insurance Institution using *ICD* code K90	Mucosal villous atrophy	2004–2006	1,273	43.6
	Turku	Dietary grants in the Social Insurance Institution using *ICD* code K90	Mucosal villous atrophy	2004–2006	712	40.5
Virta et al. (59)	Finland (nationwide)	Dietary Grant Registry (maintained by Social Insurance Institution) with *ICD* code K90	ESPGAN criteria (1990)	2005–2014	12,847	33.1[b]
Midhagen et al. (63)	Sweden (Örebro)	1) Departments of Medicine and Pediatrics registries 2) Dietitian register	Mucosal lesions with malabsorption, history of CD, and histologic improvement with gluten-free diet	1976–1986	129	8.7
Sher et al. (17)	United Kingdom (Leicestershire, England)	1) Leicester hospital records 2) Questionnaires to general practitioners 3) The Coeliac Society	Cluysenaer and van Tongren criteria	1975–1989	82	2.4[b]

Table 3. (*continued*)

Study	Country (area)	Case ascertainment	Diagnostic criteria	Period	New cases	Incidence (per 100,000)
Hawkes et al. (19)[a]	United Kingdom (Cardiff and Vale of Glamorgan, Wales)	1) Cardiff teaching hospital records 2) Hospital activity data 3) Questionnaires to general practitioners/hospital consultants 4) Questionnaire to the Coeliac Society	ESPGAN criteria (1990)	1981–1995	110	2.2[b]
Hurley et al. (20)[a]	United Kingdom (Cardiff and Vale of Glamorgan, Wales)	1) Cardiff and the Vale of Glamorgan hospital records 2) Letters to National Health Service and private hospitals practitioners/hospital consultants 3) Hospitals outside area contacted to identify patients in geographic boundaries	ESPGHAN criteria (1990)	1996–2005	305	8.8[b]
West et al. (21)	United Kingdom (nationwide)	Clinical Practice Research Datalink: Read codes J690.00, J690.13, J690z00, J690100, J690.14, J690000	Not stated	1990–2011	7,768	14.6
Southern Europe						
Tosic et al. (60)	Bosnia and Herzegovina (Tuzla)	Hospital records at the University Clinical Center Tuzla	Histological and serological confirmation	2007–2009	42	2.6
Zingone et al. (26)	Italy (Campania)	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)	2011–2013	990	7.3[b]
	Avellino	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)	2011–2013	88	8.4[b]
	Benevento	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)	2011–2013	26	3.8[b]
	Caserta	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)	2011–2013	153	7.3[b]

Table 3. (*continued*)

Study	Country (area)	Case ascertainment	Diagnostic criteria	Period	New cases	Incidence (per 100,000)
	Naples	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)	2011–2013	480	6.8[b]
	Salerno	Database (CeliaDB) created through the Campania Region Celiac Network—participating centers register previous and new diagnoses	Marsh criteria (1992)	2011–2013	243	9.3[b]
Fernandez et al. (61)	Spain (Vigo)	Hospital records from Hospital POVISA	Marsh criteria	1986–2008	68	2.0[b]
Western Europe						
Burger et al. (29)	Netherlands (nationwide)	Dutch Pathology Registry	Marsh criteria (1992)	1995–2010[d]	2,583	4.1[b]
Oceania						
Cook et al. (31)	New Zealand	Database with new diagnoses registered from gastroenterology and pediatric departments in Canterbury	Marsh type 3 lesion	1970–1999	332	4.5[b]
Northern America						
Stewart et al. (52)	Canada (Calgary)	Pathology and endoscopy databases	Modified Marsh criteria (1999)	2004–2008	518	11.6[b]
Ludvigsson et al. (34)	United States (Olmsted County)	1) Rochester Epidemiology Project 2) Electronic medical records (Mayo Clinic Life Sciences System) 3) Patient charts with *ICD-9* code 579.0	Not stated	2000–2010	189	18.3[b]

CD, celiac disease; ESPGAN, The European Society for Paediatric Gastroenterology and Nutrition; ESPGHAN, The European Society for Paediatric Gastroenterology Hepatology and Nutrition; ICD, International Classification of Diseases.
[a]Additional data provided by authors.
[b]Overall incidence calculated (see Supplementary Digital Content 2, Table S2, http://links.lww.com/AJG/B368for formula).
[c]In the absence of biopsy confirmation, justification for diagnosis provided.
[d]Represents years 1995, 2000, 2005, 2008, and 2010.

(86–88). CD was diagnosed in approximately 3% of Swedish children born between 1984 and 1996. Many of these diagnoses have been attributed to high levels of gluten fed to infants after discontinuation of breastfeeding (89,90). Two nationwide cohorts (in Norway and Denmark) have highlighted the use of antibiotics in the first year of life to increase the risk of developing CD, including a dose-gradient effect (91). Alternatively, the hygiene hypothesis, which suggests decreased exposure to microbes early in life results in an overactive immune response later in life, has been postulated as an explanation for the rising incidence of several autoimmune disorders, including CD (92,93). Other factors such as season of birth, early childhood infections, latitude, and mode of delivery have also been proposed as increasing the risk of developing CD (86,94–97). Future research is necessary to more conclusively understand the etiology of CD.

Some regions are demonstrating a stabilization or decrease in CD incidence. In Finland, adult incidence decreased by 3.4% annually from 2005 to 2014 and childhood incidence stabilized from 2008 to 2013 (37,59). After decades of fluctuating incidence in Sweden, an inflection point in 2003 indicated childhood-onset CD stabilized from 2003 to 2009 (40). As these regions represent areas with some of the highest incidence of CD, it is plausible CD has reached peak incidence in these nations. Given previous research on other gastrointestinal diseases such as inflammatory bowel disease and appendicitis,

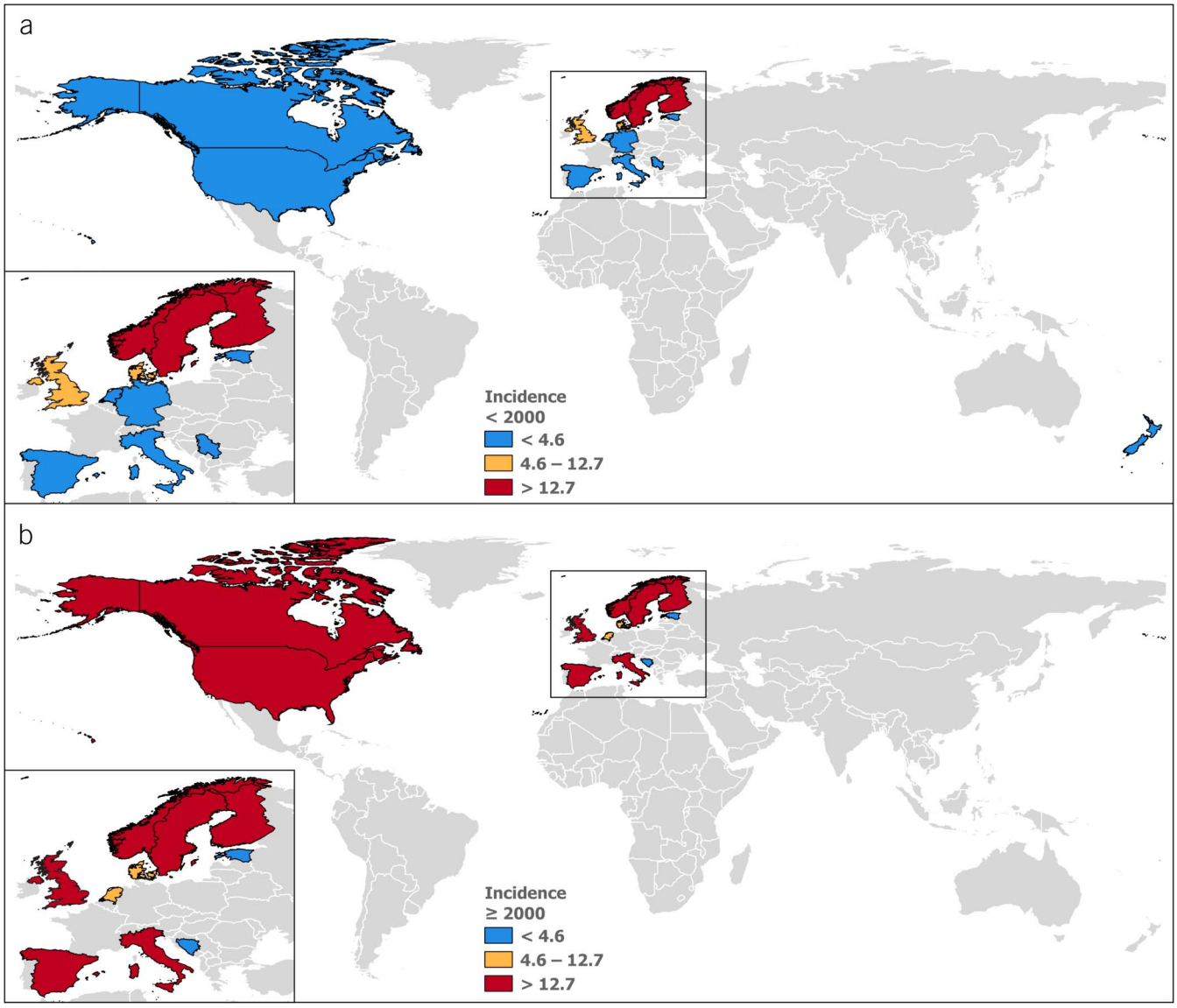

Figure 2. Geographic differences in the incidence (per 100,000 person-years) of celiac disease before 2000 (**a**) and 2000 onwards (**b**). Interactive web-based map: https://wpsites.ucalgary.ca/gilkaplan/global-celiac-disease-incidence/.

which have exhibited a stabilizing or decreasing of incidence in several industrialized countries, CD could be experiencing similar epidemiologic changes (98,99).

Alternatively, stabilizing incidence may result in part from the adoption of a gluten-free diet among those without an established diagnosis of CD (5,100). Individuals self-diagnosing a sensitivity to gluten or perceive health benefits from this dietary regime proactively remove gluten from their diet without being tested for CD. Indeed, the prevalence of individuals on a gluten-free diet without a diagnosis of CD has risen markedly in recent years (101). Furthermore, given the heritability of CD, first-degree relatives may initiate treatment of a gluten-free diet without being tested. With a proportion of those with CD remaining undiagnosed, either because they do not get tested, or they are tested when already following a gluten-free diet (thereby reducing the sensitivity of diagnostic tests), the true incidence of diagnosed CD is masked. Future epidemiologic research in countries with high incidence will help to illuminate exactly what might be leading to a stabilization or decrease in incidence.

A major gap in the literature is the paucity of population-based studies on the incidence of CD in newly industrialized countries outside the Western world. A recent meta-analysis estimated the prevalence of CD to be 0.6% in Asia, 0.5% in Africa, and 0.4% in South America (1). Global epidemiology studies have documented rapidly rising incidence of inflammatory bowel disease in several of these regions (98). An analogous rise in the incidence of CD is likely occurring as countries in these areas adopt more industrialized societies. These findings call for population-based studies to determine the frequency and changing patterns of CD over time in newly industrialized countries.

Our study has limitations. Our meta-analyses of incidence rates exhibited heterogeneity. However, given the large sample

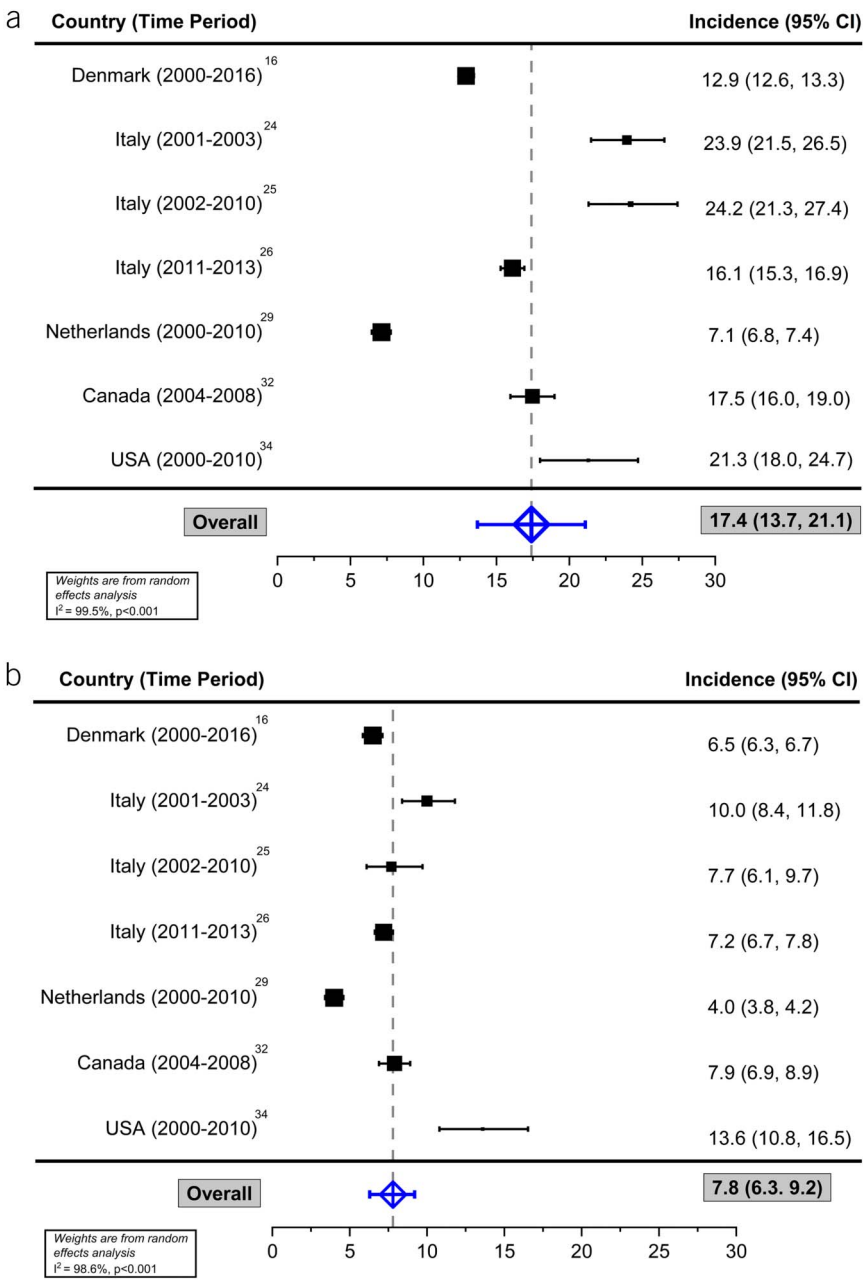

Figure 3. Pooled incidence of female (**a**) and male (**b**) celiac disease in the 21st century. CI, confidence interval.

sizes of population-based studies included in this review, there was considerable statistical power to detect differences in the incidence of CD (102). Moreover, meta-analyses of incidence rates and AAPCs differ from those assessing measures of association, thereby indicating the need for an alternative interpretation of heterogeneity (e.g., an overall incidence estimate can be used by stakeholders to compare regional incidence rates with an overall "average"). Some of the heterogeneity observed may be related to differences in diagnostic practices, data collection, and years covered, for example—but it is also likely there is genuine heterogeneity illustrating the epidemiology of CD is truly different between regions. Furthermore, many studies were restricted to specific regions and/or age groups; this makes it difficult to determine the degree in which estimates can be generalized to the overall population in certain countries. However, our quality assessment indicated a low risk of bias in most studies. Given our restriction to population-based studies, any form of selection bias was essentially eliminated. Misclassification bias was also minimized as most studies included diagnosed cases as defined by biopsy-confirmed CD.

This systematic review is the first to perform an in-depth exploration of trends in the incidence of CD over time. Our findings confirm the rate at which CD is diagnosed has significantly increased throughout many industrialized countries. However, it remains difficult to predict how these patterns will change in the coming years as some recent cohorts are seeing a stabilization of incidence. The rising recognition of CD in

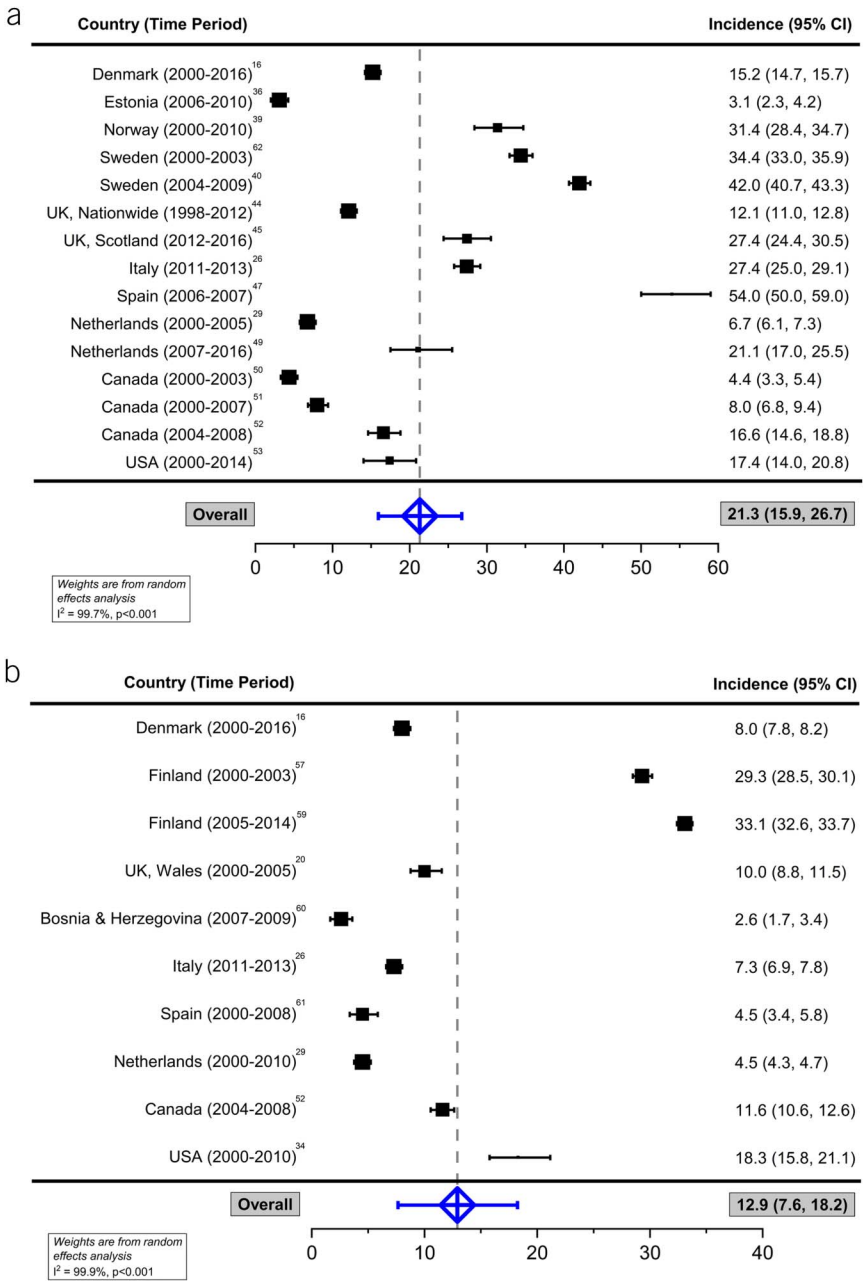

Figure 4. Pooled incidence of pediatric (**a**) and adult (**b**) celiac disease in the 21st century. CI, confidence interval.

conjunction with noninvasive serological testing has unmasked latent patients and narrowed the gap between the incidence of diagnosed cases and true incidence of CD. Regardless, a mounting incidence, of which a significant portion of those diagnosed are children, will continue to intensify the burden of CD as these cohorts continue to age. With nondietary therapies for CD undergoing clinical trials (103), disease management and treatment will soon undergo major shifts for many patients. Further population-based research should be performed in Africa, Asia, and Latin America to determine the incidence of CD in these regions. As the epidemiology of CD continues to change, and new clues into the etiology of the condition emerge, strategies to help manage and prevent CD globally can be developed.

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CONFLICTS OF INTEREST

Guarantor of the article: Gilaad G. Kaplan, MD, MPH, FRCPC.
Specific author contributions: J.A.K. and G.G.K. have full access to all data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. J.A.K., J.J., F.E.U., and G.G.K. conceived and designed the study. J.A.K., J.J., F.E.U., J.Q., N.P., J.W.W., and G.G.K. collected and analyzed the data. All authors drafted the manuscript. All authors interpreted the data and

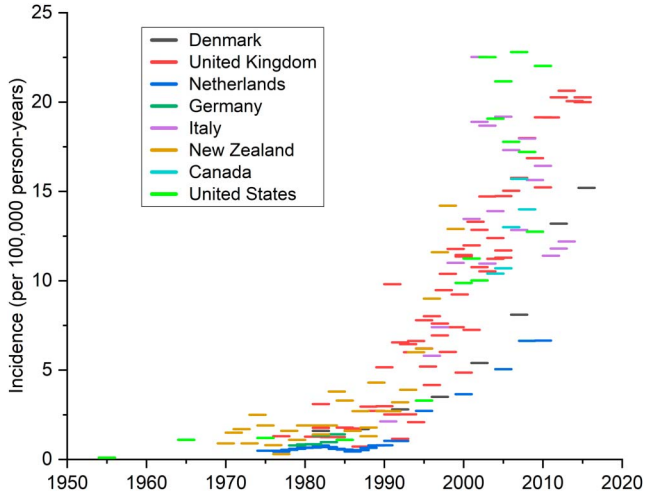

Figure 5. Trends in the incidence of celiac disease over time among all ages, by country.

provided critical revisions of the manuscript for important intellectual content. All authors have approved the final draft of the manuscript.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ The prevalence of CD is estimated to affect approximately 1% of the population, although there is variation by geographic, sex, and age categories.
- ✓ Several studies have shown an increase in CD incidence over time; however, no study has systematically evaluated temporal patterns on a global scale.

WHAT IS NEW HERE

- ✓ Studies reporting the incidence of CD come predominantly from industrialized countries.
- ✓ Although CD incidence differs geographically (e.g., high in Sweden and low in Bosnia and Herzegovina), by sex (higher in females), and by age (higher in children), there is a consistent pattern of increasing incidence over time.

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