

Temporal and geographic trends in celiac disease publications: a bibliometric analysis

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Background Despite the increasing prevalence of celiac disease (CD), the rate of diagnosis remains low. This may be related to the lack of research and publications on CD compared with other gastrointestinal conditions. We hypothesized that CD publications are underrepresented as compared with other gastrointestinal illnesses, and are particularly underrepresented in the USA.

Goal To explore the rate of CD publication output, comparing it with other gastrointestinal conditions, and to assess for changes over time.

Study We used an iterative search process to identify all articles in PubMed from 1980 to 2009, and compared the number of publications featuring CD to Crohn's disease and *Helicobacter pylori*. We analyzed CD publication output with respect to its degree of diffusion among journals and authors, and assessed for an association between economic parameters and output.

Results The number of publications has increased steadily since 1980, with acceleration in the rate of increase beginning in 1995; this trend was also observed in the number of publications in Crohn's disease, whereas the number of publications for *H. pylori* has begun to decline. The 10 journals with the largest number of Crohn's disease publications were responsible for 29% of all Crohn's disease research output in 1995–1999 and 30% in

2005–2009. In contrast, the top 10 CD journals were responsible for 34% of CD output in 1995–1999, but only 25% in 2005–2009 ($P < 0.0001$). Publication output per nation was moderately associated with gross domestic product ($r = 0.59$, $P < 0.0001$).

Conclusion The number of publications in CD is increasing, out of proportion to the overall growth of the peer-reviewed medical literature. CD publications are spread throughout a larger number of journals, but are more dominated by high-volume authors. Economic factors are associated with national contributions to the world literature in CD. *Eur J Gastroenterol Hepatol* 24:1071–1077
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Introduction

Celiac disease (CD) is an autoimmune disorder affecting genetically susceptible individuals who ingest a known environmental trigger, gluten, which is the major storage protein of wheat, rye, and barley [1]. Serologic screening studies indicate that CD is common, with prevalence rates reaching ~1% of the general population [2]. The diagnosis, though, is typically delayed [3,4]; studies have indicated a long duration of symptoms before diagnosis and delays in diagnosis attributed to physician factors [4,5,6]. Increased rates of diagnosis in the general practice setting occur when specific patient groups are screened [7]. The deficit in physician knowledge may be attributable to a lack of emphasis in the medical literature.

We aimed to investigate the state of CD publications using the method of bibliometric analysis. This methodology uses a statistical review of scientific production to assess the development of scientific information using quantitative and qualitative approaches; publication output and impact factors are commonly used end-points for quantifying the production and interpreting its effect [8].

In this study, we quantify and investigate the temporal and geographic trends in the production of CD research relative to similar digestive diseases and the overall scientific literature. We aimed to measure trends in CD research by a number of parameters including quantity, location, and impact; we also aimed to determine trends in the concentration of CD research by author, location, and journal. We hypothesized that CD publications are underrepresented as compared with other gastrointestinal illnesses, and are particularly underrepresented in the USA.

Methods

Bibliographic search

The search for publications was performed in July 2010 using the PubMed database. All papers published in 1960–2009 were evaluated.

The CD search strategy was developed by inputting 'celiac disease' in the MeSH field [mesh] and 'celiac disease' and 'celiac sprue' in the title or abstract [tiab]. The alternate spellings, 'coeliac disease' and 'coeliac sprue', were similarly searched. The final search strategy was: 1960:2009[dp] AND

('celiac disease'[MeSH] OR 'celiac disease'[tiab] OR 'coeliac disease'[tiab] OR 'celiac sprue'[tiab] OR 'coeliac sprue'[tiab]).

The comparison search for Crohn's disease was similarly performed. First, 'crohn disease' was input into the MeSH field [mesh]. Then, all variations of the spelling and the keyword 'crohn's' were input into the title–abstract search field. The final search strategy was: 1960:2009[dp] AND 'crohn disease'[MeSH] OR 'crohn*' disease'[tiab] OR 'crohns disease'[tiab] OR 'crohn's disease'[tiab] AND ('crohn*[tiab] OR 'crohns'[tiab] OR 'crohn's'[tiab]).

The second comparator, *Helicobacter pylori* research, had the search strategy: 1980:2009[dp] AND ('*helicobacter pylori*' [MeSH] OR '*pylori*'[tiab]). This MeSH term includes the term *Campylobacter pylori*, an earlier name. Almost 100% of the *H. pylori* publications were published after 1984.

Articles that were published in print in 2010 but categorized by the electronic PubMed publication date as 2009 were included. Specific analyses were conducted in the subgroups of the most recent citations, 1980:2009[dp] and 1995:2009[dp] [9].

Authors

Redundancies in individual author names were clarified by classifying the author of each publication by last name along with up to two initials of the first and middle names. The ambiguity of different authors with the same first and last names was considered when compiling the list of most prolific authors [9].

Impact factor

Impact factor, produced by the Institute for Scientific Information, represents the average number of citations per article published in a science journal. It is often used to compare the relative importance of journals within a scientific field [10]. To attribute an impact factor to each journal, the 2009 edition of the *Journal Citation Reports* was used [11]. The quality of CD research in 1995–2009 was quantified as the product of the number of publications produced and that journal's impact factor. For certain enterprises, individual journals and their respective impact products were calculated and then added together to represent the publisher more accurately; for example, Nature Publishing Group included all *Nature* journals.

Countries

The origin of the CD research by country was attributed by the affiliation of the first author of that article. A manual search of country of origin was performed for the 8224 CD publications from 1990 to 2009, yielding a designated affiliation for 99.9% of the research; the few remaining publications with unknown origins were excluded from the analysis.

To further compare countries, the effects of country size and the heterogeneous availability of resources were

considered. The number of CD publications was analyzed with respect to the gross domestic product (GDP), population size, and GDP-per-capita. Demographic and economic data for each country were retrieved from the International Monetary Fund [12] and the US Census Bureau [13].

Statistical analysis

Comparisons in proportions were performed using the χ^2 -test and, when applicable, the Cochran–Armitage test for trend. Linear correlation was measured using Pearson's correlation coefficient. *P* values of less than 0.05 were considered statistically significant. All statistical calculations were performed using SAS version 9.2 (SAS Inc., Cary, North Carolina, USA).

Results

Historical trends

Publication search from PubMed in 1960–2009 retrieved 13 911 CD and 30 356 Crohn's disease citations. From 1984 to 2009, 29 610 *H. pylori* citations were retrieved. More than half of the total CD and Crohn's disease citations were produced in 1995–2009: 7056 CD citations, accounting for 50.7% of the total, and 17 359 Crohn's disease citations, comprising 57.2% of the total. The number of CD articles published worldwide increased from 25 in 1960 to 275 in 1995, peaking at 722 in 2009. Similarly, the number of Crohn's disease publications started at 68 in 1960, increased to 700 in 1995, and reached 2021 in 2009. In contrast, the number of *H. pylori* publications started at one in 1984, increased until its peak of 2000 in 2002, and thereafter decreased through 2009. Publication analysis for these three gastrointestinal disorders showed separate trends (Fig. 1).

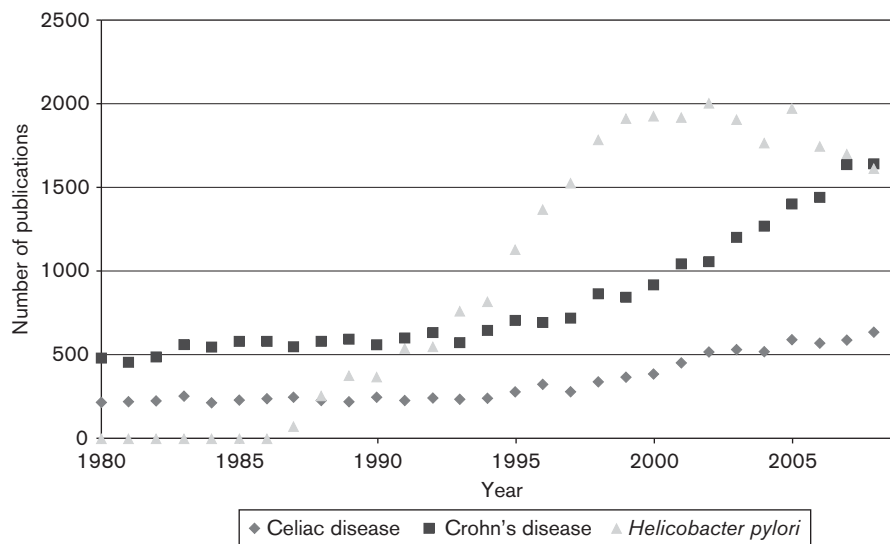
Comparison with overall scientific production

Along with the absolute growth of CD research, the percentage of CD publications relative to overall scientific production has also increased. In 1995–1999, CD publications comprised 0.07% of all PubMed publications; in 2000–2004 and 2005–2009, in contrast, CD research comprised 0.09% (*P* for trend < 0.0001). A similar increase was observed in the percentage of Crohn's disease citations, increasing from 0.17% of all PubMed publications in 1995–1999 to 0.25% in 2005–2009. The number of *H. pylori* publications, as mentioned earlier, not only decreased from its peak in the early 2000s, but declined relative to the overall scientific production as well from 0.35% of PubMed publications in 1995–1999 to 0.26% in 2005–2009.

Journal concentration

The 7056 CD publications produced in 1995–2009 were categorized into 1120 unique scientific journals. Many of these journals published only a single article on CD, and only 293 of these journals published five or more articles.

Fig. 1



Comparative trend of celiac disease, Crohn's disease, and *Helicobacter pylori* research annually from 1980 to 2009.

The 10 journals with the highest number of CD publications are listed in Table 1.

During that period, the concentration of CD research published by the top-10 highest-producing journals decreased, as measured for each 5-year time block within that interval (Table 2). From 1995 to 1999, 1580 CD articles in 410 distinct journals were published, of which 33.9% were published by the top 10 producers. This figure progressively decreased to 24.6% in the last 5-year period (P for trend < 0.0001), indicating wider dissemination among more journals. This trend was not observed in Crohn's disease research publications during the same time periods; the percentage published remained stable (P for trend = 0.0797).

Authors

CD research was more concentrated in 1995–2009 by its top 10 most prolific authors than was Crohn's disease research (Table 3). In 1995–1999, 198 CD articles were produced or collaborated on by one of the top-10 highest-producing authors, comprising 12.5% of the 1580 total. This percentage decreased in 2000–2004 to 11.7% and returned to 12.5% in the last period (P for trend = 0.8880). Crohn's disease research, however, was less concentrated by its highest-producing authors. This varied from 7.2 to 9.0% and 6.7% in the above time frames (P for trend = 0.0504).

Number of publications by country

Seventy-nine countries published 8224 CD articles in 1990–2009. Italy, the USA, and the UK were the most prolific producers, publishing 1490, 1128, and 1030

Table 1 The top-10 highest-publishing celiac disease research journals during the time period of 1995–2009 by number of PubMed publications

Journal title	Number of publications
<i>Journal of Pediatric Gastroenterology and Nutrition</i>	276
<i>The American Journal of Gastroenterology</i>	254
<i>Gut</i>	231
<i>Scandinavian Journal of Gastroenterology</i>	214
<i>European Journal of Gastroenterology & Hepatology</i>	182
<i>Gastroenterology</i>	167
<i>Digestive Diseases and Sciences</i>	150
<i>Digestive and Liver Disease</i>	127
<i>Journal of Clinical Gastroenterology</i>	107
<i>Acta Paediatrica</i> (Oslo, Norway: 1992)	100

articles, respectively (Table 4). Together, these three nations comprised 44.4% of the total CD research. Only 10 of the 79 countries produced at least 200 articles, and these countries combined to produce 72.7% of all CD. From 1990 to 2009, the overall proportion of CD research arising from the USA was 12.5%. This percentage increased consistently from 9.0% in 1990–1994 to 10.8% in 1995–1999, to 13.8% in 2000–2004, and to 16.9% in 2005–2009 ($P < 0.0001$).

There was a moderate correlation between publication output and overall GDP ($r = 0.59$, $P < 0.0001$). This correlation was weaker ($r = 0.30$, $P = 0.03$) when the top three producers were excluded. However, publication output was not shown to correlate with GDP-per-capita ($r = 0.04$, $P = 0.78$) or with population size ($r = 0.04$, $P = 0.76$). The results for GDP-per-capita remained the same even after the top three producers were excluded ($r = 0.05$, $P = 0.75$) as did the results for population ($r = -0.02$, $P = 0.89$).

Table 2 Concentrations in the percentage of celiac disease and Crohn's disease research published by the top-10 respective highest-producing journals for each 5-year time period in the interval of 1995–2009

Year	Total celiac disease articles	Percent of celiac disease research by its top 10 journals (%)	Total Crohn's disease articles	Percent of Crohn's disease research by its top 10 journals (%)
1995–1999	1580	33.9	3795	29.0
2000–2004	2382	30.8	5453	29.0
2005–2009	3094	24.6	8111	30.4

P-value for celiac disease research, *P*<0.0001; *P*-value for Crohn's disease research, *P*=0.0797.

Table 3 Concentration by percentage of celiac disease and Crohn's disease research by top-10 highest-producing authors/collaborators

Year	Number of celiac disease articles	Number of celiac disease articles by a top-10 author	Percentage of celiac disease articles by a top-10 author or collaborator (%)	Number of Crohn's disease articles	Number of Crohn's disease articles by a top-10 author or collaborator	Percentage of Crohn's disease articles by a top-10 author or collaborator (%)
1995–1999	1570	198	12.5	3795	273	7.2
2000–2004	2363	278	11.7	5453	489	9.0
2005–2009	3076	386	12.5	8111	544	6.7

P-value for celiac disease trend, *P*=0.8880; *P*-value for Crohn's disease trend, *P*=0.0504.

Table 4 List of the highest-producing countries of celiac disease research by number of publications during the period of 1995–2009, minimum 20 publications

Country	<i>N</i> (1990–2009)
Italy	1490
USA	1128
UK	1030
Spain	441
Germany	388
Sweden	334
France	332
Finland	316
Netherlands	314
Canada	205
Norway	179
Australia	160
Turkey	153
India	142
Israel	141
Ireland	123
Poland	121
Argentina	109
Brazil	104
Czech Republic	100
Hungary	86
Russia	82
Austria	81
Switzerland	78
Denmark	75
Tunisia	64
Belgium	44
Japan	38
Greece	37
Iran	29
Chile	27
Mexico	22

Publication quality

The top 20 journals ranked by impact product are listed in Table 5. Of these, several with the highest assigned overall impact factor by the *Journal of Citation Reports* for any biomedical scientific publication are included, such as *Lancet*, *The New England Journal of Medicine*, *Nature*, and *JAMA*. Although most of these journals are international producers or based in the USA, notable exceptions

include the *British Medical Journal* and the *Scandinavian Journal of Gastroenterology*. Finally, although nearly all of these highest-impact journals for CD research are nonspecialized, the *Journal of Pediatric Gastroenterology* and the journal *Neurology* are notable for their pediatric and neurological focuses, respectively.

Discussion

We confirmed our hypothesis that CD is underrepresented in the medical literature, as its publication output trails behind that of Crohn's disease, which is considerably less common than CD. However, we found encouraging countervailing trends: CD publications are growing out of proportion to the medical literature as a whole, the representation of the USA in the CD literature is increasing over time, and CD publications are being diffused in a wide variety of journals.

The course of the recent progress in CD research is notable. Its pace has accelerated in the last 15 years, even when compared with Crohn's disease research, which has shown a similar 50-year increase in output and a comparable, but slightly flatter, 15-year increase. The growth of the Internet may explain the increase in CD and Crohn's disease research observed starting in the mid-1990s. In December of 1995, for example, there were only 16 million Internet users worldwide, or 0.4% of the world's population, whereas in December of 2009, there were 1.8 billion users, or 26.6% of the population [14]. This technological revolution contributed toward biomedical research for many reasons, including better access to information as well as increased global communication and collaboration. Of relevance to this study, the Internet provides accessibility to online publication databases and therefore a greater output of globally published research. The global nature of CD research is reflected in the wide geographic distribution of CD research production.

Table 5 Table of top 20 celiac disease research journals with the highest impact products (number of publications × impact factor) for the time period 1995–2000

Journal title	Number of celiac disease publications	Impact factor (IF)	Product of number and IF
<i>Lancet</i>	86	30.758	2645.188
<i>The New England Journal of Medicine</i>	48	47.05	2258.4
<i>Gut</i>	231	9.357	2161.467
<i>Gastroenterology</i>	167	12.899	2154.133
<i>The American Journal of Gastroenterology</i>	254	6.012	1527.048
<i>Nature Publishing Group</i>	38	Amalgam (main journal IF = 34.48)	642.937
<i>Journal of Pediatric Gastroenterology and Nutrition</i>	276		602.508
<i>BMJ (Clinical Research ed.)</i>	41		560.06
<i>Scandinavian Journal of Gastroenterology</i>	214		445.976
<i>Alimentary Pharmacology and Therapeutics</i>	98	4.357	426.986
<i>Digestive and Liver Disease</i>	127	2.972	377.444
<i>JAMA</i>	12	28.899	346.788
<i>Gastrointestinal Endoscopy</i>	51	6.713	342.363
<i>Clinical Gastroenterology and Hepatology</i>	55	5.642	310.31
<i>European Journal of Gastroenterology & Hepatology</i>	182	1.662	302.484
<i>Digestive Diseases and Sciences</i>	150	1.838	275.7
<i>Journal of Clinical Gastroenterology</i>	107	2.207	236.149
<i>Endoscopy</i>	37	5.545	205.165
<i>Neurology</i>	24	8.172	196.128
<i>Clinical and Experimental Immunology</i>	65	3.009	195.585

The relative increase in CD and Crohn's disease research, expressed by higher percentages of PubMed publications, reflects a change in interest in these diseases. This interest is particularly notable in the USA, which produced increasingly greater percentages of the total global research for CD, despite the otherwise increased globalization that is observed for total gastrointestinal disease research between 1980 and 2005 [15]. Increased CD interest is also apparent in contrast to *H. pylori* research. As *H. pylori* was only first investigated in the early 1980s, it is not surprising that its publications increased rapidly until 2002. The ensuing decline in publications, both absolutely and relatively, however, likely represents a saturation in interest.

Recent interest in CD could be because of its changing disease burden. 'Disease burden' is the WHO method of assessing the mortality and loss of health because of diseases [16]. The association between CD burden and research output is supported by the data showing that the 10 countries that combined to produce most of the CD research (73% in 1990–2009) all have a prevalence of ~1%. This group of top 10 most prolific countries includes the USA and many European – especially Western and Northern – countries, where CD is one of the most common lifelong diseases [17], with a rate of prevalence similar to the current estimates for the USA [2]. Increased disease burden does not just spark research interest, but more research funding as well [18].

The burden of disease, though, reflects only the prevalence of diagnosed disease. Although the majority of those with CD are undiagnosed [19], there has been an increase in the rate of diagnosis as diagnostic techniques improve [20,21]. Greater medical and public awareness, in addition, create an environment in which more

physicians test for CD and more of the general population recognize their symptoms and undergo testing. These factors may have contributed toward the increased disease burden, but the actual, undiagnosed, prevalence of CD – not just a reflection of detection or awareness – has also been increasing over the past several decades. [18] The prevalence of CD, as determined by serological screening of stored sera, has been shown to have increased four-fold in the US over a 50-year time period [22], with a similar increase discovered in Finland [23]. Although the exact etiology of the increase in incidence is beyond the scope of this paper, environmental causes such as changes in the processing or consumption of cereal grains [24] or in childhood infection and autoimmunity are more likely than human genetic shifts, which occur slowly to environmental challenges [18]. Still, CD publications comprise about one-third of Crohn's disease publications, whereas Crohn's disease is far less common [25], albeit that it too is increasing in prevalence [26,27].

The increase in CD research published in nongastrointestinal journals in 1995–2009 [28] reflects the growing understanding of CD as a multisystem disease and that its nonclassical presentations predominate [3]. For example, the journal *Neurology* is represented in the top-20 CD journals with the highest impact products. Crohn's disease also presents with extraintestinal symptoms, most commonly affecting the eyes, skin, joints, kidneys, liver and biliary tracts, and vasculature [29]. Roughly 30% of its research, though, was produced by its top-10 highest-producing journals from 1995 to 2009, possibly because its most common symptoms are diarrhea and abdominal pain, whereas the extraintestinal manifestations often accompany those classical symptoms. Therefore, research

of even the atypical presentations of Crohn's disease would fit into the spectrum of GI-focused journals.

CD, formerly considered a predominantly pediatric disease, is now recognized as mainly an adult disorder. The *Journal of Pediatric Gastroenterology and Nutrition*, however, was noted to be the journal with the most CD publications, reflecting a persistent interest among pediatric gastroenterologists together with a relative lack of interest among adult gastroenterology researchers. This is supported by the concentration of publications among fewer authors.

This study has several limitations. The publication's country of origin, for example, was based on the affiliation of the first author, a methodology that may not accurately represent multicountry collaborations. The large numbers of publications included in this analysis, however, dilute the classification challenge that international collaborations present. In addition, these research partnerships typically rotate the first-author positions on their various publications [9]. Another limitation of PubMed may involve a bias toward English-language studies, thereby underestimating the role of certain countries known to print in their original languages – China, Japan, and Russia, for example [30].

Another limitation of PubMed is its imprecise categorization of research into clinical or basic science research, as well as separating original research, case presentations, and literature reviews. In this analysis, therefore, all types of scientific literature were included, an approach that may be misleading in the form of CD research that has been conducted. Finally, although citation frequency, through impact factor in particular, is the most common method for evaluating the effect of scientific research, it is contested and may not be the true indicator of the significance of research.

This study presents the analysis of temporal and geographic trends in CD research, as compared with two other digestive diseases. The number of publications in CD is increasing, out of proportion to the overall growth of the peer-reviewed medical literature. Compared with Crohn's disease, CD publications are spread throughout a larger number of journals, but are more dominated by high-volume authors. Economic factors are associated with national contributions to the world literature in CD. Given the growth in the number of CD publications and the increased diversity of journals in which these publications appear, gastroenterologists and other clinicians are more likely to encounter CD publications now than in previous years. This may lead to increased awareness and diagnosis rates, resulting in the improved care of patients with CD.

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Conflicts of interest

Dr Green is a consultant for Shire and Alba Therapeutics, and serves on the scientific advisory board of Alvine Pharmaceuticals.

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