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Incidence and Prevalence of Celiac Disease and Dermatitis Herpetiformis in the UK Over Two Decades: Population-Based Study

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OBJECTIVES: **Few studies have quantified the incidence and prevalence of celiac disease (CD) and dermatitis herpetiformis (DH) nationally and regionally by time and age groups. Understanding this epidemiology is crucial for hypothesizing about causes and quantifying the burden of disease.**

METHODS: **Patients with CD or DH were identified in the Clinical Practice Research Datalink between 1990 and 2011. Incidence rates and prevalence were calculated by age, sex, year, and region of residence. Incidence rate ratios (IRR) adjusted for age, sex, and region were calculated with Poisson regression.**

RESULTS: **A total of 9,087 incident cases of CD and 809 incident cases of DH were identified. Between 1990 and 2011, the incidence rate of CD increased from 5.2 per 100,000 (95% confidence interval (CI), 3.8–6.8) to 19.1 per 100,000 person-years (95% CI, 17.8–20.5; IRR, 3.6; 95% CI, 2.7–4.8). The incidence of DH decreased over the same time period from 1.8 per 100,000 to 0.8 per 100,000 person-years (average annual IRR, 0.96; 95% CI, 0.94–0.97). The absolute incidence of CD per 100,000 person-years ranged from 22.3 in Northern Ireland to 10 in London. There were large regional variations in prevalence for CD but not DH.**

CONCLUSIONS: **We found a fourfold increase in the incidence of CD in the United Kingdom over 22 years, with large regional variations in prevalence. This contrasted with a 4% annual decrease in the incidence of DH, with minimal regional variations in prevalence. These contrasts could reflect differences in diagnosis between CD (serological diagnosis and case finding) and DH (symptomatic presentation) or the possibility that diagnosing and treating CD prevents the development of DH.**

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INTRODUCTION

Population-based estimates of the incidence and prevalence of a disease are crucial for investigating the possible reasons for its occurrence and any changes in its underlying risk factors, but perhaps more importantly to quantify the likely burden upon healthcare systems and society in general (1). For celiac disease (CD), numerous studies have been able to quantify the seroprevalence of positive anti-endomysial antibodies and/or anti-tissue transglutaminase antibodies in single populations and at single points in time (2). With some variation, the overall seroprevalence has been surprisingly constant at around 1% in most populations studied (3). This has not been the same for clinically recognized and diagnosed disease where disparities exist across time, place, and individual characteristics, which indicates that there are opportunities for improving diagnostic pathways and health outcomes (4–9).

Although many epidemiological studies on the incidence and prevalence of clinically diagnosed CD have been carried out, relatively few have spanned long periods of time, in the same population, and studied both CD and dermatitis herpetiformis (DH) together (9). Those that have been published (10–15) are very small, have not included all age groups (16), are neither population based nor nationwide (having focussed on, for example, only US military personnel (17) or specific regions of a country (4,18)), and have used variable disease definitions (19). Some incidence studies among children have shown a two- to threefold

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increase in incidence of CD in Denmark and Sweden over a 13-year period (5,8), and another study in Scotland has shown a sixfold increase over 20 years (20), but no general population-based longitudinal data (over multiple decades) are available for all regions of a nation for adult CD. Similar information for DH is not so readily available, but the information that is available mainly comes from Finland and suggests that DH is becoming less common (21,22). This reduction is in direct contrast to CD (4,14) and would be a surprising result if confirmed, as both CD and DH are thought to share underlying pathophysiology. However, one intriguing possible explanation of such divergent trends might be that less exposure to gluten following a diagnosis of CD prevents DH from developing, as originally proposed by Salmi *et al* (22).

To quantify the incidence and prevalence of clinically diagnosed CD and DH and to make comparisons with the known seroprevalence, we carried out a large population-based study across all regions of the United Kingdom using routinely available electronic medical data. We have therefore been able to determine variations in incidence and prevalence by age, sex, geographical region, and calendar time over a 22-year period.

METHODS

Study population

Data were extracted from the Clinical Practice Research Datalink (CPRD; version July 2012) accessed under the University of Nottingham's CPRD license. These data contain electronic information on consultations, diagnoses, and prescriptions delivered in primary care in the United Kingdom, and have been validated for a wide variety of diagnoses (23). The accuracy of the diagnosis of CD in CPRD has also been specifically validated against medical records that were obtained previously for a sample of individuals and shown to be good (24). For this study, we used patients who were registered at a practice at some point from 1 January 1990 to 31 December 2011 inclusive. This data set contains ~57 million person-years of available data for analysis among 12 million contributing patients within 644 general practices, and it is generally representative of the population of the United Kingdom. Within the data set, patients are labeled as 'acceptable' for use in research, and data recorded do not raise concerns about validity and are recorded to the high research standard defined by CPRD. For this study, we only used 'acceptable' patients. This study was approved by the Independent Scientific Advisory Committee of the CPRD (protocol 12_106R).

We identified people with Read codes (25) representing CD (J690.00 celiac disease; J690.13 gluten enteropathy; J690z00 celiac disease NOS; J690100 acquired celiac disease; J690.14 sprue-nontropical; J690000 congenital celiac disease) or DH (M140.00 DH; M145200 senile DH; M142.00 juvenile DH). Patients could have a diagnosis of both CD and DH. The incidence and prevalence for each diagnosis was calculated separately, as described below. The date of the earliest recorded code for CD or DH was considered as the date of diagnosis for each case patient.

Cases were classified as incident if their first code representing CD or DH occurred at least 12 months after the patient's date of registration with the general practitioner (GP) and after the first date of up-to-standard data for the general practice. All other cases were considered prevalent. The methodology underpinning these definitions are described in full elsewhere (24), have been used in other studies of CD using these data (26) and of incidence of other chronic gastrointestinal diseases i.e., inflammatory bowel disease (27,28).

Statistical analysis

We calculated crude incidence of CD and DH by dividing the number of newly diagnosed cases of each disease by the total follow-up time in the study period (1990–2011). We stratified disease incidence by sex, age group (categorized *a priori* as 0–4 years, 5–17, 18–29, 30–49, 50–69 years, and 70 years and over), calendar year, socioeconomic status of the area in which the general practice resides where the patient was registered (quintiles by rank of Indices of Multiple Deprivation), and region of residence (defined based on the location of the practice as either one of the 10 regions of England mapping to the government offices of the regions, or the other countries forming the United Kingdom: Wales, Scotland, or Northern Ireland). The age categories were selected *a priori*, and children were separated into under 5 years and 5–18 years, as previous literature has shown a peak in incidence for children under 5 years of age. Incidence rates were presented per 100,000 person-years with a Poisson model fitted to determine incidence rate ratios (IRR). These IRRs were fully adjusted for sex, age group, calendar year, and region of residence. Likelihood ratio tests were used to test for departure from linear trend for calendar year.

Point prevalence of CD or DH was calculated for the 30 of June 2011, using all cases (both incident and prevalent) that were diagnosed before or on this date and who were still alive and registered with a participating practice. We then divided by the total CPRD population for acceptable registered patients at that date and calculated a percentage of the population with either CD or DH, and the respective 95% confidence intervals (CIs). We then applied our prevalence and incidence results to the estimated general population in the United Kingdom to predict the current numbers living with CD and DH (and newly diagnosed) in 2011 in the whole of the United Kingdom based on our findings.

Subgroup analyses. We examined the trends in the incidence of CD in a number of subgroups. First, we identified all patients who also had a diagnosis of another autoimmune disorder such as type 1 diabetes or thyroid disease. Second, we identified patients with symptoms of weight loss or diarrhea, or those who had a diagnosis of anemia in the year before diagnosis. Finally, we identified all patients who had an endoscopy within a year of diagnosis. For this latter analysis, we restricted the population to those patients who had linked data from Hospital Episodes Statistics available between 2000 and 2010.

Sensitivity analyses. For the first sensitivity analysis, we repeated all our analyses restricting our case populations to those who,

in addition to one diagnostic record of either CD or DH, had a relevant prescription for a gluten-free product and/or dapsone and/or a second documented record of their disease. As a second sensitivity analysis only for DH, we broadened the case definition to include CD patients as additional DH patients if they were found to have a prescription for dapsone (but without a DH diagnostic code).

Stata version 12 (Stata Statistical Software, College Station, TX) was used for all statistical analyses.

RESULTS

A total of 9,087 incident cases of CD and 809 incident cases of DH were identified between 1990 and 2011, equating to an overall incidence rate of 13.8 per 100,000 person-years for CD and 1.2 per 100,000 person-years for DH. There were 220 cases with an incident diagnosis of both DH and CD during the study period, equating to an incidence of 0.3 per 100,000 person-years.

Incidence of CD

Stratified incidence rates of CD by sex, age group, calendar year, socioeconomic status, and region of residence are displayed in **Table 1**. Incidence of CD was nearly twice as high in female individuals as in male individuals: adjusted IRR, 1.85 (95% CI (1.78, 1.94)). Incidence of CD by age showed a typical bimodal distribution, with incidence rates highest in people less than 5 years of age and aged between 50 and 69 years (**Table 1**). The incidence increased overall across the 22-year period studied from 5.2 to 19.1 per 100,000 person-years (trend IRR, 1.06 (1.05–1.06), $P<0.0001$ adjusted for age, gender, region, and socioeconomic status), but this masked a significant interaction with age (likelihood ratio test $P<0.0001$; **Figure 1**). Incidence in those under 5 years of age remained relatively constant across the period studied: IRR, 1.01 (95% CI (0.99, 1.03), $P<0.0001$) (linear model for year adjusted for sex and region). Incidence in 5–29-year-olds increased annually by almost 10% each year, 5–17-year-olds, adjusted IRR, 1.09, 95% CI, 1.08–1.11, $P<0.0001$); and 18–29-year-olds, adjusted IRR, 1.09 (95% CI, 1.07–1.10, $P<0.0001$). Incidence in those aged 30 years and more increased more moderately at ~4–7% a year. There was marked regional variation in incidence, with a significantly higher incidence seen in Northern Ireland (absolute incidence 22.3 per 100,000 person-years; **Figure 2**). The lowest incidence was reported in the London region (absolute incidence 10 per 100,000 person-years). CD incidence was also higher among patients registered at general practices located in less socioeconomically deprived areas.

Incidence of DH. Stratified incidence rates of DH by sex, age group, calendar year, and region of residence are displayed in **Table 2**. Incidence of DH was almost identical in male and female individuals: adjusted IRR, 0.99 (95% CI (0.87, 1.14)). Incidence of DH by age did not show as distinct a bimodal distribution as did CD, although incidence in those aged under 5 years was greater than in those aged between 5 and 29 years (**Table 2**). Incidence was highest in those aged 50–69 years, as in CD. Incidence decreased overall across the 22-year period studied from 1.82 to 0.80 per 100,000 person-years (**Figure 3**), representing a −4% change in incidence per year (IRR adjusted for sex, age group, and region and socioeconomic status, 0.96 (95% CI (0.94, 0.97), $P<0.0001$); there was no significant interaction between age and year (likelihood ratio test, $P=0.3562$)). There was, however, modest regional variation in incidence, with absolute rates being highest in the Yorkshire and the Humber region (**Figure 4**). There was no clear pattern of DH incidence by socioeconomic quintile.

Prevalence of CD and DH. On 30 June 2011, there were 10,872 people with CD who were alive and contributing data, which corresponded to a point prevalence of 0.24% across the entire population or 1 in every 420 people. The prevalence was substantially higher in female individuals than in male individuals, and it increased with increasing age. The prevalence of DH was much lower at 0.03% ($n=1,160$) across the entire population or 1 in every 3,300 people. On 30 June 2011, 411 people had a diagnosis of both DH and CD (prevalence = 0.01%) (**Table 3**).

Our data set covers ~6% of the English population. On the basis of our prevalence rates, this equates to ~150,000 people living with CD and ~19,000 people living with DH in the United Kingdom in 2011. On the basis of our incidence rates, we estimate that ~12,000 of those with CD and 500 with DH had been newly diagnosed in that year.

Subgroup analyses. First, we examined the trends in incidence of CD with an autoimmune disease of either type 1 diabetes or thyroid disease. The prevalence of a diagnosis of either type 1 diabetes or thyroid disease among those with CD was around 0.9% and 1.3%, respectively. The increase in the incidence of CD with either of these comorbidities (trend IRR, 1.06 (1.05–1.07), $P<0.0001$) was unchanged from that of CD overall (IRR, 1.06 (1.05–1.06), $P<0.0001$; both estimates adjusted for age, gender, region, and socioeconomic status).

Second, the proportion of CD patients who had symptoms of weight loss or diarrhea recorded in the previous year doubled over the study period from 25 to 51%. The increase in the incidence of this subgroup (adjusted trend IRR, 1.10 (1.09–1.11), $P<0.0001$) was greater than that for CD overall. There was a similar increase in the proportion (from 18 to 53%) and the incidence of CD, with anemia recorded in the year before diagnosis (adjusted trend IRR, 1.13 (1.12–1.13), $P<0.0001$).

Third, we identified any recording of a gastroscopy within a year of diagnosis for the subset of cases from primary care practices linked to HES between 2000 and 2010 (63% of English practices). The proportion of CD diagnoses with a recorded endoscopy increased from 63 to 72%, and after adjusting for age, gender, region, and socioeconomic status the trend persisted (trend IRR, 1.11 (1.10–1.12), $P<0.0001$).

Sensitivity analyses. The results for incidence overall stratified by year when we restricted our CD case population to only

Table 1. Incidence of celiac disease

	Cases	Person-years	Incidence rate (per 100,000 person-years) (95% CI)		
All	**9,087**	**65,856,848**	**13.80**	**(13.52, 14.08)**	**Incidence rate ratio[a] (95% CI)**
Sex					
Male	3,137	32,679,920	9.60	(9.27, 9.94)	1.00 (ref)
Female	5,950	33,176,929	17.93	(17.48, 18.40)	1.85 (1.78, 1.94)
Age group					
<5	390	2,550,088	15.29	(13.81, 16.89)	1.00 (ref)
5–17	929	10,140,413	9.16	(8.58, 9.77)	0.59 (0.52, 0.66)
18–29	809	8,922,980	9.07	(8.45, 9.71)	0.59 (0.53, 0.67)
30–49	2,768	19,716,119	14.04	(13.52, 14.57)	0.91 (0.82, 1.01)
50–69	2,916	16,041,746	18.18	(17.52, 18.85)	1.15 (1.03, 1.28)
70+	1,275	8,485,502	15.03	(14.21, 15.87)	0.91 (0.82, 1.02)
Year					
1990	51	988,225	5.16	(3.84, 6.79)	1.00 (ref)
1991	95	968,428	9.81	(7.94, 11.99)	1.84 (1.31, 2.58)
1992	75	1,145,736	6.55	(5.15, 8.21)	1.23 (0.86, 1.75)
1993	84	1,302,251	6.45	(5.15, 7.99)	1.22 (0.86, 1.72)
1994	93	1,402,018	6.63	(5.35, 8.13)	1.25 (0.89, 1.76)
1995	117	1,502,788	7.79	(6.44, 9.33)	1.46 (1.05,2.03)
1996	137	1,707,438	8.02	(6.74, 9.49)	1.50 (1.09, 2.07)
1997	155	2,037,465	7.61	(6.46, 8.90)	1.42 (1.03, 1.95)
1998	241	2,320,549	10.39	(9.12, 11.78)	1.93 (1.43, 2.62)
1999	322	2,732,415	11.78	(10.53, 13.14)	2.19 (1.63, 2.94)
2000	367	3,230,521	11.36	(10.23, 12.58)	2.11 (1.58, 2.83)
2001	422	3,522,256	11.98	(10.86, 13.18)	2.23 (1.66,2.98)
2002	485	3,773,659	12.85	(11.73, 14.05)	2.38 (1.79,3.18)
2003	578	3,927,535	14.72	(13.54, 15.97)	2.72 (2.04,3.62)
2004	504	4,066,850	12.39	(11.33, 13.52)	2.29 (1.72, 3.06)
2005	617	4,184,895	14.74	(13.60, 15.95)	2.73 (2.05, 3.63)
2006	636	4,228,443	15.04	(13.89, 16.26)	2.78 (2.09, 3.70)
2007	673	4,270,604	15.76	(14.59, 17.00)	2.92 (2.20, 3.88)
2008	768	4,269,975	17.99	(16.74, 19.30)	3.34 (2.51, 4.43)
2009	722	4,282,448	16.86	(15.65, 18.14)	3.13 (2.36, 4.16)
2010	808	4,218,998	19.15	(17.85, 20.52)	3.56 (2.68, 4.73)
2011	790	4,127,638	19.14	(17.83, 20.52)	3.55 (2.68, 4.72)
Region					
North East	146	1,355,821	10.77	(9.09, 12.66)	1.00 (ref)
North West	1,121	8,425,342	13.31	(12.54, 14.11)	1.18 (0.99, 1.40)
Yorkshire and The Humber	383	2,993,984	12.79	(11.54, 14.14)	1.22 (1.01, 1.48)
East Midlands	396	2,758,331	14.36	(12.98, 15.84)	1.36 (1.12, 1.64)
West Midlands	796	5,786,860	13.76	(12.82, 14.75)	1.21 (1.01, 1.45)
East of England	799	6,441,340	12.40	(11.56, 13.30)	1.08 (0.90, 1.29)
South West	778	4,994,795	15.58	(14.50, 16.71)	1.30 (1.08, 1.55)

Table 1 continued on the following page

Table 1. Continued

	Cases	Person-years	Incidence rate (per 100,000 person-years) (95% CI)		
All	**9,087**	**65,856,848**	**13.80**	**(13.52, 14.08)**	**Incidence rate ratio[a] (95% CI)**
South Central	1,035	7,061,717	14.66	(13.78, 15.58)	1.15 (0.97, 1.38)
London	715	7,183,686	9.95	(9.24, 10.71)	0.85 (0.71, 1.02)
South East Coast	777	5,613,311	13.84	(12.89, 14.85)	1.14 (0.95, 1.36)
Northern Ireland	510	2,292,558	22.25	(20.36, 24.26)	1.88 (1.56, 2.27)
Scotland	887	5,253,856	16.88	(15.79, 18.03)	1.36 (1.14, 1.62)
Wales	744	5,695,248	13.06	(12.14, 14.04)	1.11 (0.93, 1.32)
SES quintile					
1 (Least deprived)	1,909	12,297,158	15.52	(14.84, 16.24)	1.00 (ref)
2	1,841	12,531,110	14.69	(14.03, 15.38)	0.97 (0.91, 1.04)
3	1,788	12,874,502	13.89	(13.25, 14.55)	0.92 (0.86, 0.98)
4	1,978	14,983,975	13.20	(12.63, 13.80)	0.89 (0.84, 0.95)
5 (Most deprived)	1,571	13,170,103	11.93	(11.35, 12.53)	0.83 (0.77, 0.89)

Exact/each year was included in the Poisson model as categorical, as there was a significant departure from linear trend (likelihood ratio test, P=0.0001).
[a]Adjusted for all other variables in the table.

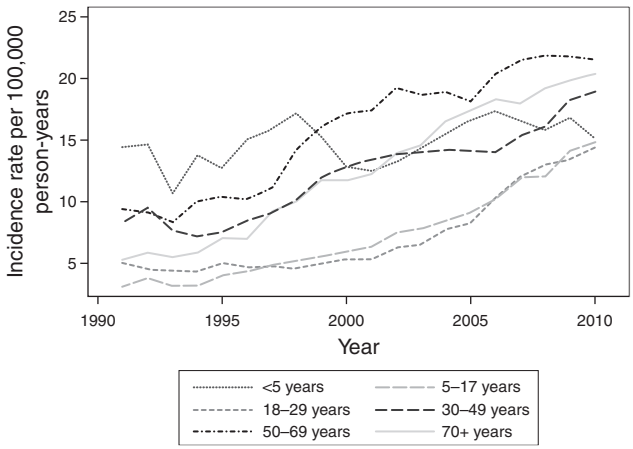

Figure 1. Three-year rolling average incidence of celiac disease (CD) in the period 1990–2011, by age group.

those individuals with a gluten-free or dapsone prescription or more than one diagnostic code are shown in **Figure 5**. These results indicate that there was a 17% reduction in our estimated CD prevalence and a 23% reduction in our CD incidence rates by using this method. This reduction in the estimates did not vary greatly by age at diagnosis, but it did increase each year and varied by region in a similar way to the overall trends of CD for the full study. For example, the reduction in incidence varied by year from 14% in 1990 to 20% in 2010, and there was considerable variation by region, from 13% in Yorkshire and Humber to 34% in London. However, despite this the overall trend in the increase of CD, incidence persisted (trend IRR, 1.05 (1.04–1.05), $P<0.0001$, adjusted for age, gender, region, and socioeconomic status).

The results for incidence overall stratified by year when we restricted our DH case population to only those individuals with a dapsone prescription or more than one diagnostic code, or broadened the DH case population to include CD with a dapsone prescription, are shown in **Figure 6**. These results indicate that broadly there was a 30–40% reduction in our estimated DH prevalence and incidence rates using the restricted population. However, even within this sensitivity analysis, the overall trend in the decrease of DH incidence persisted (trend IRR, 0.96 (0.94–0.97), $P<0.0001$, adjusted for age, gender, region, and socioeconomic status).

DISCUSSION

We found that across the 22-year period of our study, there was a near fourfold increase in the incidence of CD in the United Kingdom, which contrasted starkly with a 4% annual decrease in the incidence of DH. We observed some regional variation in both diseases across the United Kingdom, with Northern Ireland and Yorkshire and the Humber having the highest incidence rates of CD and DH, respectively, and noted that CD occurred more commonly among areas with least socioeconomic deprivation. Our figures for prevalence estimate that about 3 in 10,000 children under 5 years of age currently in the United Kingdom have been diagnosed with CD, with this figure increasing to 4 in 1,000 adults over the age of 70 years. For DH, the prevalence estimates are ~10-fold lower. On the basis of our incidence figures,

Figure 2. Map of incidence of celiac disease (CD) by regional government office.

we estimate that in 2011 ~12,000 people were newly diagnosed with CD and 500 with DH in the United Kingdom.

Our study is the largest population-based study of the occurrence of both CD and DH, to date, providing accurate incidence and prevalence rates for all ages and across a longer calendar period than has previously been reported. Key to any measure of incidence is the method of defining the cases being counted as new diagnoses. In this study, we have defined a new case when an individual's GP records a first diagnosis of either CD or DH in their medical record. Such diagnoses in the United Kingdom are not made without a referral to secondary care and the diagnostic investigations inherent within that process (29–32). We believe that this assumption is valid, as previously we have investigated the accuracy of the diagnosis of CD recorded electronically by GPs, by reviewing the medical paper records including correspondence and results that emanated from secondary care (24). The agreement was improved in that validation study(24) by insisting, within a more restrictive case definition, on each individual having a prescription for a gluten-free product or a second record of their disease. This case definition increased the specificity; a positive predictive value for a single code was 81%, for a gluten-free prescription it was 89%, and for two diagnostic codes it was 100%. However, this had the disadvantage of reducing the sensitivity of our case definition. We therefore used a single diagnostic code to maximize the sensitivity in the main analysis of our current study and used the more specific definition in the sensitivity analysis. We found that 80% of celiac patients had a prescription for a gluten-free product or multiple codes, which was entirely consistent with external data in previously published surveys of local regions and populations. First, Hall *et al.* (33) conducted a questionnaire study of a sample of CD patients identified by Read codes in north east England, and reported that only 86% received a gluten-free prescription. In addition, only 3% of those identified who returned the questionnaire stated that they did not have CD, which provides additional evidence to support our use of Read codes in defining CD. Furthermore, Coeliac UK's commercial team surveyed their own members in 2012 and found that only 75% of members were using gluten-free prescriptions (Coeliac UK (2012)) Prescriptions Report), and in May 2013 a repeat survey in Oxford found that 80% of their members used gluten-free prescriptions (Coeliac UK (2013) Impact Oxfordshire Report). Our study's finding for the whole of the United Kingdom that about 80% of CD patients are having a gluten-free prescription is therefore what would be expected.

It is possible that we would have underestimated our DH incidence rates if doctors have not recorded this additional diagnosis in people with CD as well. We assessed this potential bias by including CD patients with a dapsone prescription (but no diagnostic record of DH) in our sensitivity analysis. The incidence rates for DH when we did this, however, remained broadly similar to those from comparable studies, and thus we think that it is unlikely to have introduced a large bias.

When trying to assess the incidence or prevalence of any chronic disease such as CD or DH, it is not possible to identify the moment of biological onset but rather the date of acquisition of a diagnosis. Our definition of incidence relies on the fact that a GP will record the diagnosis of a new disease at the time the diagnosis is made, i.e., representing the real world of clinical practice. Measuring the incidence and prevalence of a disease requires an unbiased, general population-based sample from which the cases can arise and be counted. In that regard, we are fortunate that the CPRD is, broadly speaking, representative of the UK population as a whole. The only group of people that seems to be underrepresented in our population are those aged 18–25 years, which may be because people in this age group are more mobile (34). This could have led to an

Table 2. Incidence of dermatitis herpetiformis

	Cases	Person-years	Incidence rate (per 100,000 person-years) (95% CI)		
All	**809**	**65,856,848**	**1.23**	**(1.15, 1.32)**	**Incidence rate ratio[a] (95% CI)**
Sex					
Male	395	32,679,920	1.21	(1.09, 1.33)	1.00 (ref)
Female	414	33,176,929	1.25	(1.13, 1.37)	0.99 (0.87, 1.14)
Age group					
<5	18	2,550,088	0.71	(0.42, 1.12)	1.00 (ref)
5–17	47	10,140,413	0.46	(0.34, 0.62)	0.66 (0.39, 1.14)
18–29	61	8,922,980	0.68	(0.52, 0.88)	0.97 (0.57, 1.64)
30–49	223	19,716,119	1.13	(0.99, 1.29)	1.61 (0.99, 2.59)
50–69	311	16,041,746	1.94	(1.73, 2.17)	2.78 (1.73, 4.48)
>69	149	8,485,502	1.76	(1.49, 2.06)	2.51 (1.54, 4.10)
Year					
1990	18	988,225	1.82	(1.08, 2.88)	0.96 (0.94, 0.97)[b]
1991	24	968,428	2.48	(1.59, 3.69)	
1992	26	1,145,736	2.27	(1.48, 3.33)	
1993	21	1,302,251	1.61	(1.00, 2.47)	
1994	20	1,402,018	1.43	(0.87, 2.20)	
1995	21	1,502,788	1.40	(0.87, 2.14)	
1996	29	1,707,438	1.70	(1.14, 2.44)	
1997	30	2,037,465	1.47	(0.99, 2.10)	
1998	35	2,320,549	1.51	(1.05, 2.10)	
1999	47	2,732,415	1.72	(1.26, 2.29)	
2000	49	3,230,521	1.52	(1.12, 2.01)	
2001	48	3,522,256	1.36	(1.00, 1.81)	
2002	52	3,773,659	1.38	(1.03, 1.81)	
2003	52	3,927,535	1.32	(0.99, 1.74)	
2004	26	4,066,850	0.64	(0.42, 0.94)	
2005	50	4,184,895	1.19	(0.89, 1.58)	
2006	56	4,228,443	1.32	(1.00, 1.72)	
2007	44	4,270,604	1.03	(0.75, 1.38)	
2008	43	4,269,975	1.01	(0.73, 1.36)	
2009	45	4,282,448	1.05	(0.77, 1.41)	
2010	33	4,218,998	0.78	(0.54, 1.10)	
2011	33	4,127,638	0.80	(0.55, 1.12)	
Region					
North East	8	1,355,821	0.59	(0.25, 1.16)	1.00 (ref)
North West	108	8,425,342	1.28	(1.05, 1.55)	2.15 (1.05, 4.42)
Yorkshire and The Humber	64	2,993,984	2.14	(1.65, 2.73)	3.37 (1.61, 7.05)
East Midlands	36	2,758,331	1.31	(0.91, 1.81)	2.03 (0.94, 4.38)
West Midlands	71	5,786,860	1.23	(0.96, 1.55)	2.07 (1.00, 4.31)
East of England	74	6,441,340	1.15	(0.90, 1.44)	1.84 (0.88, 3.84)
South West	52	4,994,795	1.04	(0.78, 1.37)	1.69 (0.80, 3.58)

Table 2 continued on the following page

Table 2. Continued

	Cases	Person-years	Incidence rate (per 100,000 person-years) (95% CI)		
All	**809**	**65,856,848**	**1.23**	**(1.15, 1.32)**	**Incidence rate ratio[a] (95% CI)**
South Central	89	7,061,717	1.26	(1.01, 1.55)	2.22 (1.07, 4.61)
London	75	7,183,686	1.04	(0.82, 1.31)	1.86 (0.89, 3.87)
South East Coast	62	5,613,311	1.10	(0.85, 1.42)	1.88 (0.89, 3.94)
Northern Ireland	27	2,292,558	1.18	(0.78, 1.71)	2.18 (0.98, 4.81)
Scotland	72	5,253,856	1.37	(1.07, 1.73)	2.50 (1.20, 5.20)
Wales	71	5,695,248	1.25	(0.97, 1.57)	2.12 (1.02, 4.41)
SES quintile					
1	153	12,297,158	1.24	(1.05, 1.46)	1.00 (ref)
2	144	12,531,110	1.15	(0.97, 1.35)	0.93 (0.74, 1.17)
3	180	12,874,502	1.40	(1.20, 1.62)	1.15 (0.92, 1.44)
4	164	14,983,975	1.09	(0.93, 1.28)	0.86 (0.69, 1.09)
5	168	13,170,103	1.28	(1.09, 1.48)	1.01 (0.81, 1.27)

Year was included in the model as a continuous variable, as there was no significant departure from a linear trend (likelihood ratio test, P=0.1886).
[a]Adjusted for all other variables in the table.
[b]Model fitted a linear trend. IRR=1 year increase in calendar time.

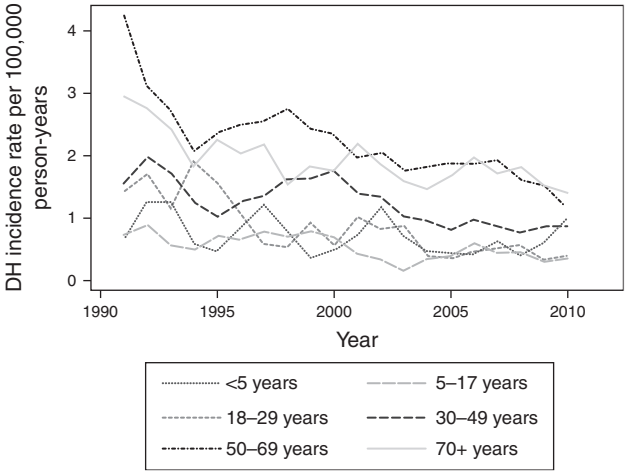

Figure 3. Three-year rolling average incidence rates of dermatitis herpetiformis (DH) in the period 1990–2011, by age group.

overestimate of the occurrence of disease in this age group in our study if those with disease are motivated to remain actively registered with a GP, regardless of their location, and are counted therefore in the numerator, in contrast to individuals in that age group who are healthy and may not register with a GP on relocation and therefore not appear in the denominator.

Prior studies on the incidence and prevalence of clinically diagnosed CD and DH in the general population that are comparable to our own are scarce (9), and all have a smaller sample size. Most studies have focussed on either CD or DH separately rather than describing the occurrence of both diseases drawn from the same population, or they have focussed on either children or adults or have reported only incidence or prevalence. Four population-based studies from Sweden (8), Denmark (5), and Scotland, United Kingdom (6,20) have measured the incidence of CD in children using information from the whole of these nations. In Swedish children under the age of 15 years, the reported annual rates increased from 19 to 44 per 100,000 over the period 1998–2003 for the whole country. The authors speculate that this particularly high rate was a consequence of high gluten consumption. By contrast, in Denmark, the rates among children under the age of 18 ranged from 2.8 to 12.3 per 100,000 in the period 1999–2008. In Scotland, the annual age- and sex-standardized incidence rate reported for children under the age of 16 years between 2009 and 2010 was 10 per 100,000 (6). When we also restricted our population to only Scottish practices, 2009 to 2010, under the age of 16 years, we found a comparable rate of 12.3 (95% CI, 8.5–17.3) per 100,000 peson-years. Of the previously published studies, only the Danish study quantified prevalence reporting that in 2010 this was 84 per 100,000 person-years or 0.08%, which was similar to our own equivalent finding of 90 per 100,000 person-yeras (prevalence in <18-year olds on 1 January 2010).

Our trends over time in adult CD diagnosis rates and prevalence were similar to three regional studies: two from the United Kingdom (18,35,36) and one in the United States (27). First, the numbers of diagnoses made and rates calculated in and around the city of Derby, UK showed a five- to sixfold increase in the absolute numbers of adults diagnosed between 1990 and 2006, which is not dissimilar to our own reported relative increase in incidence rates (35,36) Equally, an estimated prevalence from this area at the end

Figure 4. Map of incidence of dermatitis herpetiformis (DH) by regional government office.

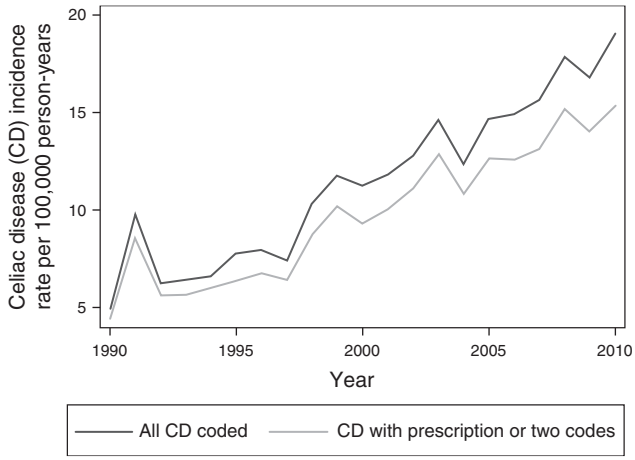

Figure 5. Incidence of celiac disease (CD) overall, and when the definition is restricted to either two diagnostic codes or a gluten-free prescription.

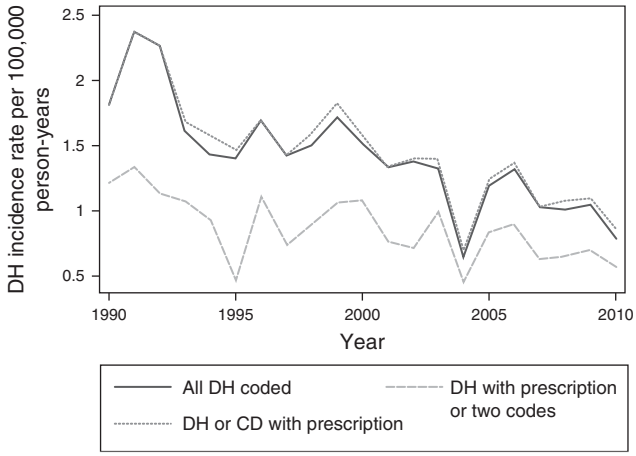

Figure 6. Incidence of dermatitis herpetiformis (DH) overall, the restricted definition to either two diagnostic codes or a dapsone or gluten-free prescription, and the broader definition including celiac disease (CD) patients with a prescription for dapsone.

of 1999 was around 0.14% (24) and was similar to our estimate of 0.11% for 1999. Second, a small study of CD incidence in East Dorset, UK, found an increase from 6.0 to 13.3 per 100,000 person-years in 1993–2002, which was also similar to our national estimates (18). In contrast, the third study from the United States showed a plateau of diagnosis rates in the past 6 years of their study (2004–2010), potentially indicating a ceiling to CD case finding through clinical presentation.

Other studies have reported incidence in adults, but these are mostly from periods before the beginning of our study period or among selected populations, therefore hindering valid comparisons. In the United States, for example, among military personnel, a low rate of 3.5 per 100,000 person-years was observed, and between 1999 and 2008 the rates increased 5–10-fold; however, this occupational population was relatively young and considered reasonably healthy by the authors (17).

For DH, the most comprehensive study is that from Finland by Salmi *et al.*, (22) which measured incidence over a 30-year period (following an original report in 2007 (21)) and elegantly summarized the existing literature before its publication They observed an overall annual incidence rate among children and adults, which decreased substantially over the period of the study from 5.2 to 2.7 per 100,000 person-years in the period 1970–2009. Our rates were lower but showed a similar rate of decline. Previous prevalence

Table 3. Point prevalence of celiac disease and dermatitis herpetiformis, 30 June 2011

	Celiac disease (*n*)	Prevalence (%)	95% CI	Dermatitis herpetiformis (*n*)	Prevalence (%)	95% CI
Overall	**10,872**	**0.24**	**(0.24, 0.25)**	**1,160**	**0.03**	**(0.02, 0.03)**
Sex						
Male	3,662	0.16	(0.16, 0.17)	560	0.03	(0.02, 0.03)
Female	7,210	0.32	(0.31, 0.32)	600	0.03	(0.02, 0.03)
Age group						
<5	93	0.03	(0.03, 0.04)	7	0.00	(0.00, 0.00)
5–17	903	0.13	(0.13, 0.14)	38	0.01	(0.00, 0.01)
18–29	1,026	0.15	(0.14, 0.16)	64	0.01	(0.01, 0.01)
30–49	2,952	0.23	(0.22, 0.24)	245	0.02	(0.02, 0.02)
50–69	3,948	0.37	(0.36, 0.38)	491	0.05	(0.04, 0.05)
70+	1,950	0.38	(0.36, 0.40)	315	0.06	(0.05, 0.07)
Region						
North East	171	0.22	(0.18, 0.25)	22	0.03	(0.02, 0.04)
North West	1,267	0.24	(0.22, 0.25)	121	0.02	(0.02, 0.03)
Yorkshire and The Humber	276	0.26	(0.23, 0.30)	47	0.04	(0.03, 0.06)
East Midlands	226	0.28	(0.24, 0.32)	23	0.03	(0.02, 0.04)
West Midlands	944	0.25	(0.23, 0.27)	91	0.02	(0.02, 0.03)
East of England	819	0.23	(0.22, 0.25)	86	0.02	(0.02, 0.03)
South West	1,072	0.28	(0.26, 0.30)	106	0.03	(0.02, 0.03)
South Central	1,408	0.25	(0.24, 0.26)	148	0.03	(0.02, 0.03)
London	905	0.16	(0.15, 0.17)	87	0.02	(0.01, 0.02)
South East Coast	1,019	0.23	(0.22, 0.25)	82	0.02	(0.01, 0.02)
Northern Ireland	592	0.39	(0.36, 0.42)	67	0.04	(0.03, 0.06)
Scotland	1,203	0.27	(0.26, 0.29)	166	0.04	(0.03, 0.04)
Wales	970	0.22	(0.21, 0.24)	114	0.03	(0.02, 0.03)

estimates from the 1970s (22) onward in Europe and the United States range from 10 per 100,000 person-years or 0.01% to 75 per 100,000 person-years in the Finnish study or 0.075%, a range that includes our own overall estimate of 0.03%.

Although we believe that the close correlation of our results with previous data, as well as the robustness of our methodology, should reassure readers that our results are correct, there are two major findings that need to be further explained. These findings are, first, the marked regional and socioeconomic variations in CD but not DH, and second the contrasting increase in CD while DH decreased. Our findings of considerable regional and socioeconomic variation in incidence rates may indicate either that there is true variation in incidence or that ascertainment of disease varies. The lowest regional incidence was seen in London, and a true variation in incidence by population characteristics such as ethnicity and mobility may be a contributing factor to this lower observed incidence (34,37). However, we believe that it is more plausible that these observed variations in incidence are mediated through disparities in health-seeking behavior and access to correct diagnostic pathways. This is partly because in the more stable, less ethnically diverse populations of the United Kingdom, where data on seroprevalence of undetected CD are available, i.e., Cambridge (38), Bristol (39), and Northern Ireland (40), this is almost identical at about 1%, yet the respective regional CD incidence rates in our study were 12, 15, and 22 per 100,000 person-years, covering almost the entire range of regional incidence rates we report. These seroprevalence studies (38–40) also report very little variation in undetected CD prevalence in the United Kingdom by age and sex, suggesting that indeed health-care utilization is the most likely reason for the lower diagnosis rates in men and in certain age groups that we observed. This interpretation is also likely to be generalizable to other health-care systems in other countries, as similar disparities have been observed in Olmsted County, Minnesota (4,41) and the whole of Finland (42,43) between clinically diagnosed incidence and prevalence estimates and seroprevalence studies.

Thus, the most logical explanation for the significant increase in incidence of CD over time is that there has been a substantial improvement in the diagnostic ascertainment of CD over the period studied. For DH, the same logic can be applied, except that for this disease we would have to hypothesize that diagnostic ascertainment has become worse over time to explain the decline. Given that DH is a visible, itchy, blistering condition of extensor surfaces of the skin (44), it seems highly unlikely that the reduction in incidence that we, and others, have observed is related to a poorer pick-up rate, and thus we believe that the observed reduction is a true one. By contrast, the mechanisms by which CD is identified and diagnosed have changed and improved over our study period with the introduction of routinely available serological tests, rapid and improved access to endoscopic services, and greater awareness among patients and doctors. Therefore, the likelihood is that for CD greater ascertainment, rather than a true increase in incidence, explains our results. Of course, if ascertainment is increased when the pool of clinical disease itself is not, the observed increase in incidence would most likely occur through an increase in the diagnosis of milder or earlier cases. This leads to the speculation that the relationship between the trends over time for CD and DH were not independent, as proposed by Salmi *et al.* (22). If we consider DH to be a consequence of untreated CD *per se*, then by identifying and treating earlier and milder CD we may be preventing the skin manifestations from presenting. This is in effect proposing at an individual level, the hypothesis previously proposed at a population level to explain the decline in DH in Finland where gluten consumption has declined nationally (22,45). However, such a hypothesis requires far more evidence before it could be considered a causal explanation.

In conclusion, we have provided contemporary, population-based, precise estimates of the incidence and prevalence of both CD and DH in the United Kingdom over a 22-year period. We have quantified the likely burden of this disease on health-care systems and society in general. We have shown that the incidence of CD has risen markedly during the period of our study and that, by contrast, DH incidence has decreased. The highest incidence of CD was seen among the very young and over 50s, whereas a steadily higher incidence with increasing age was seen for DH. Twice as many women as men get diagnosed with CD, and incidence rates vary regionally and by socioeconomic area. These findings raise the possibility that inequality in the diagnostic pathways across time, place, and person exist in the United Kingdom, given that it is thought that most sections of society appear to have a reasonably similar background risk of having CD.

CONFLICT OF INTEREST

Guarantor of the article: Joe West, PhD.

Specific author contributions: Study concept and design: Joe West, Kate M. Fleming, Laila J. Tata, Timothy R. Card, and Colin J. Crooks; acquisition of data: JW; analysis and interpretation of data: Joe West, Kate M. Fleming, Laila J. Tata, Timothy R. Card, and Colin J. Crooks; drafting of the manuscript: Joe West, Kate M. Fleming, and Colin J. Crooks; critical revision of the manuscript for important intellectual content: Joe West, Kate M. Fleming, Laila J. Tata, Timothy R. Card, and Colin J. Crooks; statistical analysis: Kate M. Fleming and Colin J. Crooks; obtainment of funding: Joe West, Kate M. Fleming, Laila J. Tata, Timothy R. Card, and Colin J. Crooks; technical or material support: Colin J. Crooks; study supervision: Joe West.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Celiac disease (CD) incidence appears to be rising worldwide, and in Finland the incidence of dermatitis herpetiformis (DH) appears to be decreasing.
- ✓ Variation by age, sex, time, and geography in the United Kingdom in the incidence of CD and DH is not well documented.

WHAT IS NEW HERE

- ✓ CD incidence has increased in the United Kingdom over the past 20 years in all age groups, except those less than 5 years of age.
- ✓ DH incidence has decreased over the past 20 years in all age groups.
- ✓ There is variation in the rates of diagnosis of CD but not DH throughout the United Kingdom, suggesting that opportunities for better ascertainment could be implemented.

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