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Incidence and prevalence of coeliac disease and dermatitis herpetiformis in the UK over two decades: population-based study.

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Abbreviations: CPRD – Clinical Practice Research Datalink; IRR - Incidence Rate Ratio; 95% CI - 95% Confidence Interval; CD – Coeliac disease; DH – Dermatitis Herpetiformis

Competing interests:

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Author contribution:
6

Author contribution area	JW	KMF	LJT	TRC	CJC
study concept and design	√	√	√	√	√
acquisition of data	√				
analysis and interpretation of data	√	√	√	√	√
drafting of the manuscript	√	√			√
critical revision of the manuscript for important intellectual content	√	√	√	√	√
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7

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1 Abstract

2 Background

3 Few studies have quantified the incidence and prevalence of coeliac disease (CD) and dermatitis

4 herpetiformis (DH) nationally and regionally by time and age groups. Understanding this

5 epidemiology is crucial for hypothesising about causes and quantifying the burden of disease.

6 Methods

7 Patients with CD or DH were identified in the Clinical Practice Research Datalink between 1990 and

8 2011. Incidence rates and prevalence were calculated by age, sex, year and region of residence.

9 Incidence rate ratios (IRR) adjusted for age, sex and region were calculated with Poisson regression.

10 Results

11 9087 incident cases of CD and 809 incident cases of DH were identified. Between 1990 and 2011 the

12 incidence rate of coeliac disease increased from 5.2/100,000 (95% CI, 3.8-6.8) to 19.1/100,000 (17.8-

13 20.5) (IRR 3.6, 95% CI 2.7-4.8). The incidence of DH decreased over the same time period from

14 1.8/100,000 to 0.8/100,000 (average annual IRR 0.96, 95% CI 0.94-0.97). The absolute incidence of CD

15 per 100,000 person years ranged from 22.3 in Northern Ireland to 10 in London. There were large

16 regional variations in prevalence for CD but not DH.

17 Conclusions

18 We found a 4-fold increase in the incidence of CD in the UK over 22 years with large regional

19 variations in prevalence. This contrasted with a 4% annual decrease in the incidence of DH with

20 minimal regional variations in prevalence. These contrasts could reflect differences in diagnosis

21 between CD (serological diagnosis and case finding) and DH (symptomatic presentation) or the

22 possibility that diagnosing and treating CD prevents development of DH.

1 Keywords

2 Epidemiology; clinical practice research datalink

STUDY HIGHLIGHTS:

4 WHAT IS CURRENT KNOWLEDGE

5 • Coeliac disease incidence appears to be rising worldwide and in Finland the incidence of DH

6 appears to be decreasing.

7 • Variation by age, sex, time and geography in the UK in the incidence of coeliac disease and

8 dermatitis herpetiformis is not well documented.

9

10 WHAT IS NEW HERE

11 Coeliac disease incidence has increased in the UK over the last 20 years in all age groups except those

12 less than 5 years of age.

13 Dermatitis herpetiformis incidence has decreased over the last 20 years in all age groups.

14 There is variation in the rates of diagnosis of coeliac disease but not dermatitis herpetiformis

15 throughout the UK suggesting opportunities for better ascertainment could be implemented.

1   Introduction

2   Population based estimates of the incidence and prevalence of a disease are crucial for investigating

3   the possible reasons for its occurrence and any changes in its underlying risk factors, but perhaps

4   more importantly to quantify the likely burden upon health care systems and society in general[1]. For

5   coeliac disease (CD) numerous studies have been able to quantify the seroprevalence of positive

6   anti-endomysial antibodies and/or anti-tissue transglutaminase antibodies in single populations and

7   at single points in time[2]. With some variation, the overall seroprevalence has been surprisingly

8   constant at around 1% in most populations studied[3]. This has not been the same for clinically

9   recognised and diagnosed disease where disparities exist across time, place and individual

10   characteristics, which indicates that there are opportunities for improving diagnostic pathways and

11   health outcomes[4-9].

12   While many epidemiological studies on the incidence and prevalence of clinically diagnosed CD have

13   been carried out relatively few have spanned long periods of time, in the same population and

14   studied both CD and dermatitis herpetiformis (DH) together[9]. Those that have been published[10-15]

15   are very small, have not included all age groups[16], are neither population based nor nationwide

16   (having focussed on for example only US military personnel[17] or specific regions of a country[4 18]) and

17   have used variable disease definitions[19]. Some incidence studies among children have shown a 2 to

18   3-fold increase in incidence of CD in Denmark and Sweden over a 13 year period[5 8] and another study

19   in Scotland has shown a 6-fold increase over 20 years[20], but no general population based longitudinal

20   data (over multiple decades) are available for all regions of a nation for adult CD. Similar information

21   for dermatitis herpetiformis (DH) is not so readily available but that which is mainly comes from

22   Finland and suggests that DH is becoming less common[21 22]. This reduction is in direct contrast to CD[4]

23   [14], and would be a surprising result if confirmed, as both CD and DH are thought to share underlying

24   pathophysiology. However, one intriguing possible explanation of such divergent trends might be

1   that less exposure to gluten following a diagnosis of CD prevents DH from developing as originally

2   proposed by Salmi et al[22].

3   To quantify the incidence and prevalence of clinically diagnosed CD and DH and make comparisons

4   with the known seroprevalence we carried out a large population based study across all regions of

5   the UK using routinely available electronic medical data. We have therefore been able to determine

6   variations in incidence and prevalence by age, sex, geographical region and calendar time over a 22

7   year period.

8

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 UK, 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 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 1st January 1990 to 31st December 2011 inclusive. This dataset contains approximately 57 million person years of available data for analysis among 12 million contributing patients within 644 general practices and is generally representative of the population of the United Kingdom. Within the dataset, patients are labelled 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 Coeliac Disease; J690.13 Gluten enteropathy; J690z00 Coeliac disease NOS; J690100 Acquired coeliac disease; J690.14 Sprue-nontropical; J690000 Congenital coeliac disease) or DH (M140.00 Dermatitis herpetiformis; M145200 Senile dermatitis herpetiformis; M142.00 Juvenile dermatitis herpetiformis). 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 classed as incident if their first code representing CD or DH occurred at least 12 months after the patient's date of registration with the GP and after the first date of up-to-standard data for

1 the general practice. All other cases were considered prevalent. The methodology underpinning

2 these definitions are described in full elsewhere[24], have been used in other studies of CD using these

3 data[26] and of incidence of other chronic gastrointestinal diseases i.e. inflammatory bowel disease[27 28].

Statistical analysis

5 We calculated crude incidence of CD and DH by dividing the number of newly diagnosed cases of

6 each disease by the total follow-up time in the study period (1990-2011). We stratified disease

7 incidence by sex, age group (categorised a priori as 0-4 years, 5-17, 18-29, 30-49, 50-69 years, and 70

8 years and over), calendar year, socioeconomic status of the area in which the general practice resides

9 at which the patient was registered (quintiles by rank of Indices of Multiple Deprivation), and region

10 of residence (defined based on location of the practice as either one of the 10 regions of England

11 mapping to the government offices of the regions, or the other countries forming the UK: Wales,

12 Scotland or Northern Ireland). The age categories were selected a priori, and children were separated

13 into under 5 years and 5 – 18 years as previous literature has shown an peak in incidence for under 5

14 year olds. Incidence rates were presented per 100,000 person years with a Poisson model fitted to

15 determine incidence rate ratios (IRR). These IRRs were fully adjusted for sex, age group, calendar

16 year and region of residence. Likelihood ratio tests were used to test for departure from linear trend

17 for calendar year.

18 Point prevalence of CD or DH was calculated for the 30th of June 2011, using all cases (both incident

19 and prevalent) that were diagnosed before or on this date and still alive and registered with a

20 participating practice. We then divided by the total CPRD population for acceptable registered

21 patients at that date and calculated a percentage of the population with either CD or DH, and the

22 respective 95% confidence intervals. We then applied our prevalence and incidence results to the

23 estimated general population in the UK to predict the current numbers living with CD and DH (and

24 newly diagnosed) in 2011 in the whole of the UK based on our findings.

1   Subgroup Analyses

2   We examined the trends in the incidence of CD in a number of subgroups. First we identified all

3   patients who also had a diagnosis of another autoimmune disorder such as type 1 diabetes or thyroid

4   disease. Secondly we identified patients with symptoms of weight loss or diarrhoea, or had a

5   diagnosis of anaemia in the year before diagnosis. Finally we identified all patients who had an

6   endoscopy within a year of diagnosis. For this latter analysis we restricted the population to those

7   patients who had linked data from Hospital Episodes Statistics available (2000 – 2010).

8   Sensitivity analyses

9   For the first sensitivity analysis we repeated all our analyses restricting our case populations to those

10   who in addition to one diagnostic record of either CD or DH had a relevant prescription for a gluten-

11   free product and/or dapsone and/or a second documented record of their disease. As a second

12   sensitivity analysis just for DH we broadened the case definition to include CD patients as additional

13   DH patients if they were found to have a prescription for dapsone (but without a DH diagnostic

14   code).

15   Stata version 12 was used for all statistical analyses.

1 Results

2 A total of 9087 incident cases of CD and 809 incident cases of DH were identified between 1990 and

3 2011 equating to an overall incidence rate of 13.8 per 100,000 person years for CD and 1.2 per

4 100,000 person years for DH. There were 220 cases with an incident diagnosis of both DH and CD

5 during the study period equating to an incidence of 0.3 per 100,000 person years.

6 Incidence of coeliac disease

7 Stratified incidence rates of CD by sex, age group, calendar year, socioeconomic status, and region of

8 residence are displayed in table 1. Incidence of CD was nearly twice as high in females as in males;

9 adjusted IRR 1.85 (95%CI [1.78, 1.94]). Incidence of CD by age showed a typical bimodal distribution

10 with incidence rates highest in people less than 5 years of age and aged between 50-69 years (Table

11 1). Incidence increased overall across the 22 year period studied from 5.2 to 19.1 per 100,000

12 person years (trend IRR 1.06 (1.05 - 1.06), p < 0.0001 adjusted for age, gender, region, and

13 socioeconomic status), but this masked a significant interaction with age (likelihood ratio test

14 p<0.0001) (Figure 1). Incidence in the under 5 year old group remained relatively constant across the

15 period studied; IRR 1.01(95%CI [0.99,1.03], p < 0.0001) (linear model for year adjusted for sex and

16 region). Incidence in 5-17 year olds increased annually by almost 10% each year; 5-17 year olds

17 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-

18 1.10, p < 0.0001). Incidence in those aged 30 and over increased more moderately at approximately

19 4-7% a year. There was marked regional variation in incidence with a significantly higher incidence

20 seen in Northern Ireland (absolute incidence 22.3 per 100,000 person years) (Figure 2).   The lowest

21 incidence was reported in the London region (absolute incidence 10 per 100,000 person years).

22 Coeliac disease incidence was also higher among patients registered at general practices located in

23 less socioeconomically deprived areas.

24 Incidence of dermatitis herpetiformis

1   Stratified incidence rates of dermatitis herpetiformis by sex, age group, calendar year and region of

2   residence are displayed in table 2. Incidence of DH was almost identical in males and females;

3   adjusted IRR 0.99 (95%CI [0.87, 1.14]). Incidence of DH by age did not show as distinct a bimodal

4   distribution as did CD though incidence in those aged under 5 was greater than those aged between

5   5 and 29 years (Table 2). Incidence was highest in those aged 50-69 as in coeliac disease. Incidence

6   decreased overall across the 22 year period studied from 1.82 to 0.80 per 100,000 person years

7   (Figure 3), representing a -4% change in incidence per year (IRR adjusted for sex, age group and

8   region and socioeconomic status, 0.96 (95%CI [0.94, 0.97], p < 0.0001; there was no significant

9   interaction between age and year (likelihood ratio test p=0.3562)). There was however modest

10   regional variation in incidence with absolute rates being highest in the Yorkshire & the Humber

11   region (Figure 4). There was no clear pattern of DH incidence by socioeconomic quintile.

12   Prevalence of coeliac disease and dermatitis herpetiformis

13   At 30th June 2011 there were 10,872 people with CD alive and contributing data which corresponded

14   to a point prevalence of 0.24% across the entire population or 1 in every 420 people. The prevalence

15   was substantially higher in females than males and increased with increasing age. The prevalence of

16   DH was much lower at 0.03% (n=1160) across the entire population or 1 in every 3300 people. On

17   30th June 2011 411 people had a diagnosis of both DH and CD (prevalence = 0.01%).

18   Our dataset covers approximately 6% of the English population. Based on our prevalence rates this

19   equates to approximately 150,000 people living with CD and approximately 19,000 people living with

20   dermatitis herpetiformis in the UK in 2011. Based on our incidence rates we estimate that

21   approximately 12,000 of those with CD and 500 with DH had been newly diagnosed in that year.

22   Subgroup analyses

23   First, we examined the trends in incidence of CD with an autoimmune disease of either type 1

24   diabetes or thyroid disease. The prevalence of a diagnosis of either type 1 diabetes or thyroid disease

1   among those with CD was around 0.9% and 1.3% respectively. The increase in the incidence of CD

2   with either of these co-morbidities (trend IRR 1.06 (1.05 - 1.07), p < 0.0001) was unchanged from

3   that of CD overall (IRR 1.06 (1.05 - 1.06), p < 0.0001) (both estimates adjusted for age, gender, region,

4   and socioeconomic status).

5   Second, the proportion of CD patients who had symptoms of weight loss or diarrhoea recorded in the

6   previous year doubled over the study period from 25% to 51%. The increase in the incidence of this

7   sub group (adjusted trend IRR 1.10 (1.09 - 1.11), p < 0.0001) was greater than that for CD overall.

8   There was a similar increase in the proportion (from 18% to 53%) and the incidence of CD with

9   anaemia recorded in the year prior to diagnosis (adjusted trend IRR 1.13 (1.12 - 1.13), p < 0.0001).

10

11   Third, we identified any recording of a gastroscopy within a year of diagnosis for the subset of cases

12   from primary care practices linked to HES between 2000 and 2010 (63% of English practices). The

13   proportion of CD diagnoses with a recorded endoscopy increased from 63% to 72%, and after

14   adjusting for age, gender, region, and socioeconomic status the trend persisted (trend IRR 1.11 (1.10

15   - 1.12), p < 0.0001).

16   Sensitivity analyses

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

18   those individuals with a gluten free or dapsone prescription or more than one diagnostic code are

19   shown in figure 5. These indicate that there was a 17% reduction in our estimated CD prevalence

20   and 23% reduction in our CD incidence rates using this method. This reduction in the estimates did

21   not vary greatly by age at diagnosis, but did increase each year and varied by region in a similar way

22   to the overall trends of CD for the full study. For example the reduction in incidence varied by year

23   from 14% in 1990 to 20% in 2010, and there was considerable variation by region, from 13% in

24   Yorkshire and Humber to 34% in London. However despite this the overall trend in the increase of CD

1   incidence persisted (trend IRR 1.05 (1.04 – 1.05), p < 0.0001, adjusted for age, gender, region, and

2   socioeconomic status).

3   The results for incidence overall stratified by year when we restricted our DH case population to only

4   those individuals with a dapsone prescription or more than one diagnostic code, or broadened the

5   DH case population to include CD with a dapsone prescription are shown in figure 6. These indicate

6   that broadly there was a 30-40% reduction in our estimated DH prevalence and incidence rates using

7   the restricted population. However even within this sensitivity analysis the overall trend in the

8   decrease of DH incidence persisted (trend IRR 0.96 (0.94 – 0.97), p < 0.0001, adjusted for age, gender,

9   region, and socioeconomic status).

10

Discussion

We found that across the 22 year period of our study there was a near 4-fold increase in the incidence of CD in the UK which contrasted starkly with a 4% annual decrease in the incidence of DH. We observed some regional variation in both diseases across the UK with Northern Ireland and Yorkshire & 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 currently in the UK have diagnosed CD with this figure increasing to 4 in 1,000 adults over the age of 70. For DH the prevalence estimates are approximately 10-fold lower. On the basis of our incidence figures we estimate that in 2011 approximately 12,000 people were newly diagnosed with CD and 500 with DH in the UK.

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 general practitioner (GP) records a first diagnosis of either CD or DH in their medical record. Such diagnoses in the UK are not made without a referral to secondary care and the diagnostic investigations inherent within that process[29-32]. We believe 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 study24 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%, a gluten free prescription was 89%, and two diagnostic codes was 100%. However this had the disadvantage of reducing the sensitivity of our case definition. We therefore used a single diagnostic code to maximise 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 coeliac 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 al33 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. Additionally 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 UK 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 so we think it 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 general practitioner 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

1   CPRD is broadly speaking representative of the UK population as whole. The only group of people

2   that seems to be underrepresented in our population are those aged 18-25 which may be because

3   people in this age group are more mobile[34]. This could have led to an over estimate of the

4   occurrence of disease in this age group in our study if those with disease are motivated to remain

5   actively registered with a GP, regardless of their location, and are counted therefore in the numerator

6   in contrast to individuals in that age group who are healthy and may not register with a GP on

7   relocation and therefore not appear in the denominator.

8   Prior studies on the incidence and prevalence of clinically diagnosed CD and DH in the general

9   population that are comparable to our own are scarce[9] and all have a smaller sample size. Most

10 studies have focussed on either CD or DH separately rather than describing the occurrence of both

11 diseases drawn from the same population, or they have focussed on either children or adults or have

12 reported only incidence or prevalence. Four population based studies from Sweden[8], Denmark[5] and

13 Scotland, UK[6 20] have measured the incidence of CD in children using information from the whole of

14 these nations. In Swedish children under the age of 15 the reported annual rates increased from 19

15 – 44 per 100,000 over the period 1998 to 2003 for the whole country. The authors speculate that

16 this particularly high rate was a consequence of high gluten consumption. By contrast in Denmark

17 the rates among children under the age of 18 ranged from 2.8 - 12.3 per 100,000 1999 to 2008. In

18 Scotland the annual age- and sex-standardised incidence rate reported for children under the age of

19 16 between 2009 and 2010 was 10 per 100,0006. When we also restricted our population to only

20 Scottish practices, 2009 to 2010, under the age of 16 we found comparable rate of 12.3 (95% CI 8.5-

21 17.3) per 100,000. Of the previously published studies only the Danish one quantified prevalence

22 reporting that in 2010 this was 84 per 100,000 or 0.08%, which was similar to our own equivalent

23 finding of 90/100,000 (prevalence in <18 year olds on 1st January 2010).

24 Our trends over time in adult CD diagnosis rates and prevalence were similar to three regional

25 studies; two from the UK[18 35 36] and one in the USA[27]. First the numbers of diagnoses made and rates

1 calculated in and around the city of Derby, UK showed a 5 to 6 fold increase in the absolute numbers

2 of adults diagnosed between 1990 and 2006, not dissimilar to our own reported relative increase in

3 incidence rates[35][36]. Equally, an estimated prevalence from this area at the end of 1999 was around

4 0.14%[24] and was similar to our estimate for 1999 of 0.11%.   Second, a small study of CD incidence in

5 East Dorset, UK, found an increase from 6.0 – 13.3 per 100,000, 1993 – 2002, which was also similar

6 to our national estimates.[18] In contrast the third study from USA showed a plateau of diagnosis rates

7 in the last 6 years of their study (2004-2010) potentially indicating a ceiling to CD case finding

8 through clinical presentation.

9 Other studies have reported incidence in adults but these are mostly from periods prior to the

10 beginning of our study period or among selected populations therefore hindering valid comparisons.

11 In the US for example among military personnel a low rate of 3.5 per 100,000 was observed and

12 between 1999 and 2008 the rates increased 5 to 10 fold but this occupational population was

13 relatively young and considered reasonably healthy by the authors[17].

14 For DH the most comprehensive study is that from Finland by Salmi et al which measured incidence

15 over a 30 year period (following an original report in 2007[21]) and elegantly summarised the existing

16 literature prior to its publication[22]. They observed an overall annual incidence rate among children

17 and adults which decreased substantially over the period of the study from 5.2 to 2.7 per 100,000,

18 1970 - 2009. Our rates were lower but showed a similar rate of decline. Previous prevalence

19 estimates from the 1970s[22] onwards in Europe and the USA range from 10 per 100,000 or 0.01% to

20 75 per 100,000 in the Finnish study or 0.075%, a range that includes our own overall estimate of

21 0.03%.

22 Though we believe that the close correlation of our results with previous data, as well as the

23 robustness of our methodology should reassure that our results are correct, there are two major

24 findings that need to be further explained. These are firstly the marked regional and socioeconomic

1   variations in CD but not DH, and secondly the contrasting rise in CD while DH fell. Our findings of

2   considerable regional and socioeconomic variation in incidence rates may indicate either that there is

3   true variation in incidence or that ascertainment of disease varies. The lowest regional incidence was

4   seen in London and a true variation in incidence by population characteristics such as ethnicity and

5   mobility may be a contributing factor to this lower observed incidence[34 37].   However we believe that

6   it is more plausible that these observed variations in incidence are mediated through disparities in

7   health seeking behaviour and access to correct diagnostic pathways. Partly this is because in the

8   more stable, less ethnically diverse populations of the UK where data on seroprevalence of

9   undetected CD is available, i.e. Cambridge[38], Bristol[39] and Northern Ireland[40], this is almost identical

10   at about 1% yet the respective regional CD incidence rates in our study were 12, 15 and 22 per

11   100,000, covering almost the entire range of regional incidence rates we report. These

12   seroprevalence studies [38-40]also report very little variation in undetected CD prevalence in the UK by

13   age and sex suggesting that indeed health care utilisation is the most likely reason for the lower

14   diagnosis rates in men and in certain age groups that we observed. This interpretation is also likely

15   to be generalizable to other health care systems in other countries as similar disparities have been

16   observed in Olmsted County, Minnesota[4 41] and the whole of Finland[42 43], between clinically

17   diagnosed incidence and prevalence estimates and seroprevalence studies.

18   Thus the most logical explanation for the significant increase in incidence of CD over time is that

19   there has been a substantial improvement in the diagnostic ascertainment of CD over the period

20   studied. For DH the same logic can be applied except for this disease we would have to hypothesize

21   that diagnostic ascertainment has become worse over time to explain the decline. Given that DH is a

22   visible, itchy, blistering condition of extensor surfaces of the skin[44] it seems highly unlikely that the

23   reduction in incidence we, and others, have observed is related to a poorer pick up rate, so we

24   believe the observed reduction is a true one. By contrast the mechanisms by which CD is identified

25   and diagnosed have changed and improved over our study period with the introduction of routinely

1　available serological tests, rapid and improved access to endoscopic services and greater awareness

2　among patients and doctors. Therefore the likelihood is that for CD greater ascertainment, rather

3　than a true increase in incidence, explains our results. Of course if ascertainment is increased when

4　the pool of clinical disease itself is not, the observed increase in incidence would most likely occur

5　through an increase in the diagnosis of milder or earlier cases. This leads to the speculation that the

6　relationship between the trends over time for CD and DH were not independent as proposed by

7　Salmi et al[22]. If we consider DH to be a consequence of untreated CD per se then by identifying and

8　treating earlier and milder CD we may be preventing the skin manifestations from presenting. This is

9　in effect proposing at an individual level, the hypothesis previously proposed at a population level to

10　explain the decline in DH in Finland where gluten consumption has declined nationally[22 45]. However,

11　such a hypothesis requires far more evidence before it could be considered a causal explanation.

12　In conclusion, we have provided contemporary, population based, precise estimates of the incidence

13　and prevalence of both CD and DH in the UK over a 22 year period. We have quantified the likely

14　burden of this disease on health care systems and society in general. We have shown that the

15　incidence of CD has risen markedly during the period of our study and that, by contrast, DH incidence

16　has fallen. The highest incidence of CD was seen among the very young and over 50s whereas a

17　steadily higher incidence with increasing age was seen for DH. Twice as many women as men get

18　diagnosed with CD and incidence rates vary regionally and by socioeconomic area. These findings

19　raise the possibility that inequality in the diagnostic pathways across time, place and person exist in

20　the UK given that it is thought that most sections of society appear to have a reasonably similar

21　background risk of having CD.

1 Table 1: Incidence of coeliac disease
2 (Exact/each year was included in the Poisson model as categorical, as there was a significant
3 departure from linear trend (Likelihood ratio test p=0.0001))

	Cases	Person years	Incidence rate (per 100,000 person years) [95% CI]			Incidence rate ratio*[95% CI]
All	**9087**	**65856848**	**13.80**	**[13.52,**	**14.08]**	
Sex						
Male	3137	32679920	9.60	[9.27,	9.94]	1.00 (ref)
Female	5950	33176929	17.93	[17.48,	18.40]	1.85 [1.78,1.94]
Age group	.	.	.	.	.	
<5	390	2550088	15.29	[13.81,	16.89]	1.00 (ref)
5-17	929	10140413	9.16	[8.58,	9.77]	0.59 [0.52,0.66]
18-29	809	8922980	9.07	[8.45,	9.71]	0.59 [0.53,0.67]
30-49	2768	19716119	14.04	[13.52,	14.57]	0.91 [0.82,1.01]
50-69	2916	16041746	18.18	[17.52,	18.85]	1.15 [1.03,1.28]
70+	1275	8485502	15.03	[14.21,	15.87]	0.91 [0.82,1.02]
Year	.	.	.	.	.	
1990	51	988225	5.16	[3.84,	6.79]	1.00 (ref)
1991	95	968428	9.81	[7.94,	11.99]	1.84 [1.31,2.58]
1992	75	1145736	6.55	[5.15,	8.21]	1.23 [0.86,1.75]
1993	84	1302251	6.45	[5.15,	7.99]	1.22 [0.86,1.72]
1994	93	1402018	6.63	[5.35,	8.13]	1.25 [0.89,1.76]
1995	117	1502788	7.79	[6.44,	9.33]	1.46 [1.05,2.03]
1996	137	1707438	8.02	[6.74,	9.49]	1.50 [1.09,2.07]
1997	155	2037465	7.61	[6.46,	8.90]	1.42 [1.03,1.95]
1998	241	2320549	10.39	[9.12,	11.78]	1.93 [1.43,2.62]
1999	322	2732415	11.78	[10.53,	13.14]	2.19 [1.63,2.94]
2000	367	3230521	11.36	[10.23,	12.58]	2.11 [1.58,2.83]
2001	422	3522256	11.98	[10.86,	13.18]	2.23 [1.66,2.98]
2002	485	3773659	12.85	[11.73,	14.05]	2.38 [1.79,3.18]
2003	578	3927535	14.72	[13.54,	15.97]	2.72 [2.04,3.62]
2004	504	4066850	12.39	[11.33,	13.52]	2.29 [1.72,3.06]
2005	617	4184895	14.74	[13.60,	15.95]	2.73 [2.05,3.63]
2006	636	4228443	15.04	[13.89,	16.26]	2.78 [2.09,3.70]
2007	673	4270604	15.76	[14.59,	17.00]	2.92 [2.20,3.88]
2008	768	4269975	17.99	[16.74,	19.30]	3.34 [2.51,4.43]
2009	722	4282448	16.86	[15.65,	18.14]	3.13 [2.36,4.16]
2010	808	4218998	19.15	[17.85,	20.52]	3.56 [2.68,4.73]
2011	790	4127638	19.14	[17.83,	20.52]	3.55 [2.68,4.72]
Region						
North East	146	1355821	10.77	[9.09,	12.66]	1.00 (ref)
North West	1121	8425342	13.31	[12.54,	14.11]	1.18 [0.99,1.40]
Yorkshire & The Humber	383	2993984	12.79	[11.54,	14.14]	1.22 [1.01,1.48]
East Midlands	396	2758331	14.36	[12.98,	15.84]	1.36 [1.12,1.64]
West Midlands	796	5786860	13.76	[12.82,	14.75]	1.21 [1.01,1.45]
East of England	799	6441340	12.40	[11.56,	13.30]	1.08 [0.90,1.29]
South West	778	4994795	15.58	[14.50,	16.71]	1.30 [1.08,1.55]
South Central	1035	7061717	14.66	[13.78,	15.58]	1.15 [0.97,1.38]
London	715	7183686	9.95	[9.24,	10.71]	0.85 [0.71,1.02]
South East Coast	777	5613311	13.84	[12.89,	14.85]	1.14 [0.95,1.36]
Northern Ireland	510	2292558	22.25	[20.36,	24.26]	1.88 [1.56,2.27]
Scotland	887	5253856	16.88	[15.79,	18.03]	1.36 [1.14,1.62]
Wales	744	5695248	13.06	[12.14,	14.04]	1.11 [0.93,1.32]
SES Quintile						

1 (Least deprived)	1909	12297158	15.52	[14.84,	16.24]	1.00 (ref)
2	1841	12531110	14.69	[14.03,	15.38]	0.97 [0.91,1.04]
3	1788	12874502	13.89	[13.25,	14.55]	0.92 [0.86,0.98]
4	1978	14983975	13.20	[12.63,	13.80]	0.89 [0.84,0.95]
5 (Most deprived)	1571	13170103	11.93	[11.35,	12.53]	0.83 [0.77,0.89]

1 *adjusted for all other variables in the table

2

1 Table 2: Incidence of dermatitis herpetiformis
2 (Year was included in the model as a continuous variable, as there was no significant departure from
3 a linear trend (Likelihood ratio test p=0.1886))

	Cases	Person years	Incidence rate (per 100,000 person years) [95% CI]			Incidence rate ratio*[95% CI]
All	**809**	**65856848**	**1.23**	**[1.15,**	**1.32]**	
Sex	.	.	.	.	.	
Male	395	32679920	1.21	[1.09,	1.33]	1.00 (ref)
Female	414	33176929	1.25	[1.13,	1.37]	0.99 [0.87,1.14]
Age group	.	.	.	.	.	
<5	18	2550088	0.71	[0.42,	1.12]	1.00 (ref)
5-17	47	10140413	0.46	[0.34,	0.62]	0.66 [0.39,1.14]
18-29	61	8922980	0.68	[0.52,	0.88]	0.97 [0.57,1.64]
30-49	223	19716119	1.13	[0.99,	1.29]	1.61 [0.99,2.59]
50-69	311	16041746	1.94	[1.73,	2.17]	2.78 [1.73,4.48]
>69	149	8485502	1.76	[1.49,	2.06]	2.51 [1.54,4.10]
Year	.	.	.	.	.	
1990	18	988225	1.82	[1.08,	2.88]	0.96 [0.94,0.97]**
1991	24	968428	2.48	[1.59,	3.69]	
1992	26	1145736	2.27	[1.48,	3.33]	
1993	21	1302251	1.61	[1.00,	2.47]	
1994	20	1402018	1.43	[0.87,	2.20]	
1995	21	1502788	1.40	[0.87,	2.14]	
1996	29	1707438	1.70	[1.14,	2.44]	
1997	30	2037465	1.47	[0.99,	2.10]	
1998	35	2320549	1.51	[1.05,	2.10]	
1999	47	2732415	1.72	[1.26,	2.29]	
2000	49	3230521	1.52	[1.12,	2.01]	
2001	48	3522256	1.36	[1.00,	1.81]	
2002	52	3773659	1.38	[1.03,	1.81]	
2003	52	3927535	1.32	[0.99,	1.74]	
2004	26	4066850	0.64	[0.42,	0.94]	
2005	50	4184895	1.19	[0.89,	1.58]	
2006	56	4228443	1.32	[1.00,	1.72]	
2007	44	4270604	1.03	[0.75,	1.38]	
2008	43	4269975	1.01	[0.73,	1.36]	
2009	45	4282448	1.05	[0.77,	1.41]	
2010	33	4218998	0.78	[0.54,	1.10]	
2011	33	4127638	0.80	[0.55,	1.12]	
Region	.	.	.	.	.	
North East	8	1355821	0.59	[0.25,	1.16]	1.00 (ref)
North West	108	8425342	1.28	[1.05,	1.55]	2.15 [1.05,4.42]
Yorkshire & The Humber	64	2993984	2.14	[1.65,	2.73]	3.37 [1.61,7.05]
East Midlands	36	2758331	1.31	[0.91,	1.81]	2.03 [0.94,4.38]
West Midlands	71	5786860	1.23	[0.96,	1.55]	2.07 [1.00,4.31]
East of England	74	6441340	1.15	[0.90,	1.44]	1.84 [0.88,3.84]
South West	52	4994795	1.04	[0.78,	1.37]	1.69 [0.80,3.58]
South Central	89	7061717	1.26	[1.01,	1.55]	2.22 [1.07,4.61]

London	75	7183686	1.04	[0.82,	1.31]	1.86 [0.89,3.87]
South East Coast	62	5613311	1.10	[0.85,	1.42]	1.88 [0.89,3.94]
Northern Ireland	27	2292558	1.18	[0.78,	1.71]	2.18 [0.98,4.81]
Scotland	72	5253856	1.37	[1.07,	1.73]	2.50 [1.20,5.20]
Wales	71	5695248	1.25	[0.97,	1.57]	2.12 [1.02,4.41]
SES quintile						
1	153	12297158	1.24	[1.05,	1.46]	1.00 (ref)
2	144	12531110	1.15	[0.97,	1.35]	0.93 [0.74,1.17]
3	180	12874502	1.40	[1.20,	1.62]	1.15 [0.92,1.44]
4	164	14983975	1.09	[0.93,	1.28]	0.86 [0.69,1.09]
5	168	13170103	1.28	[1.09,	1.48]	1.01 [0.81,1.27]

1   *adjusted for all other variables in the table ** model fitted a linear trend. IRR = one year increase in calendar time.
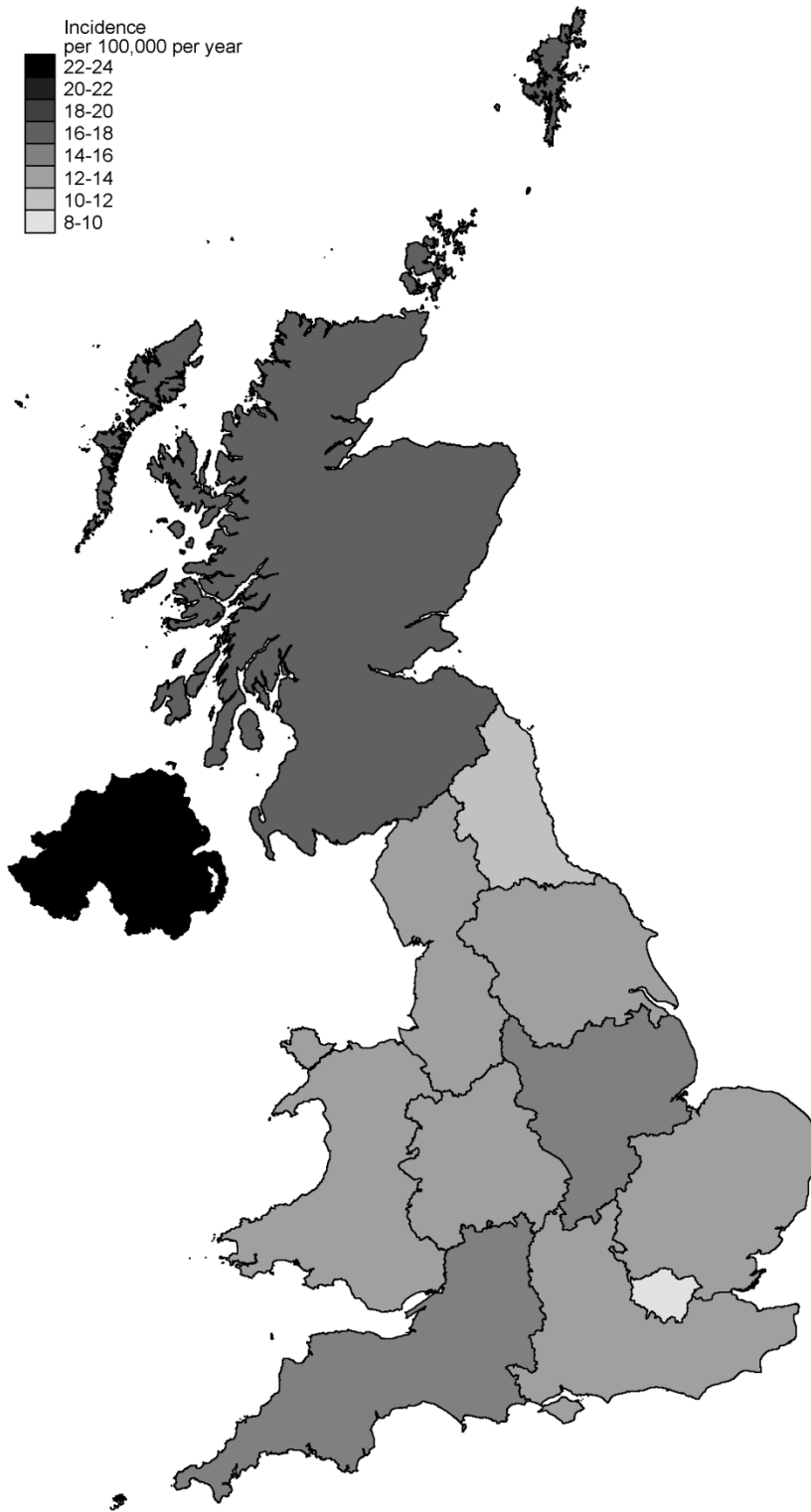
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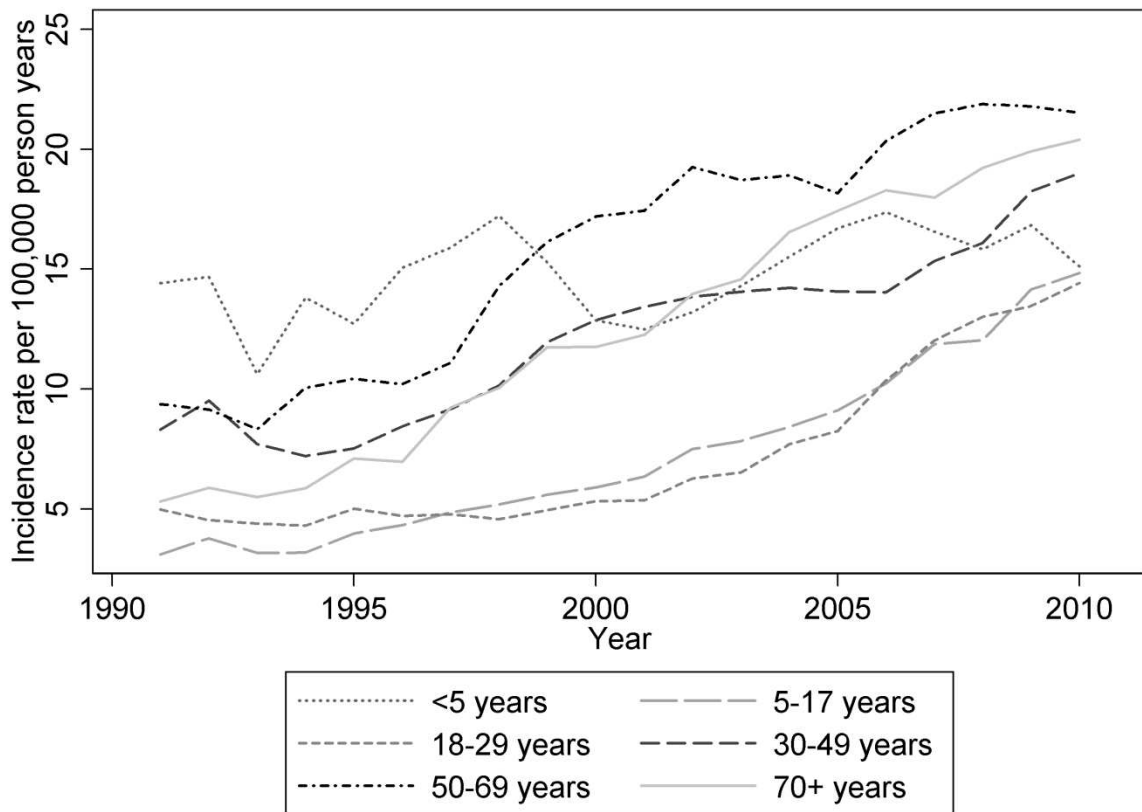
2

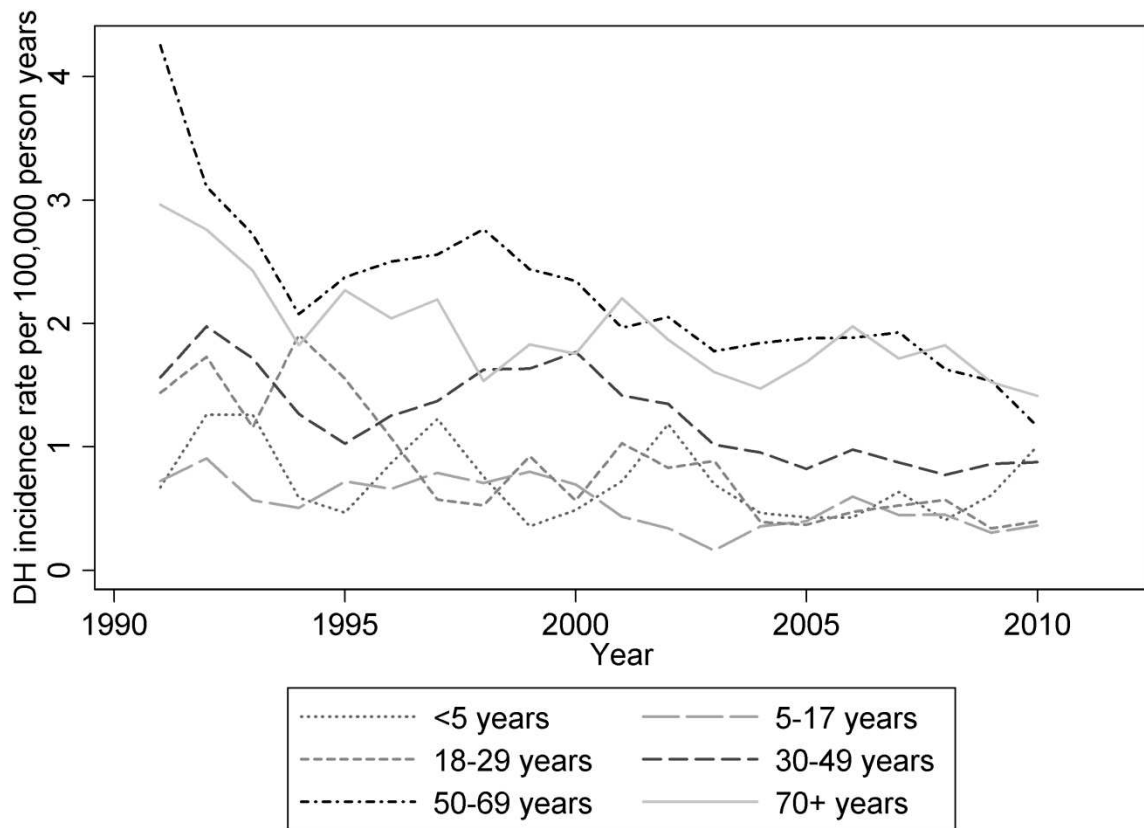3   Figure 1: 3-year rolling average incidence of coeliac disease, 1990-2011, by age group

4

Average incidence of
Coeliac disease 1990 - 2011
in England, Northern Ireland, Scotland, and Wales
(in English Regions by Government Office)

Incidence
per 100,000 per year
22-24
20-22
18-20
16-18
14-16
12-14
10-12
8-10

1

2   Figure 2: Map of incidence of coeliac disease by regional government office

1

2

3   Figure 3: 3-year rolling average incidence rates of dermatitis herpetiformis, 1990-2011, by age group

4

Average incidence of
Dermatitis Herpetiformis 1990 - 2011
in England, Northern Ireland, Scotland, and Wales
(in English Regions by Government Office)

Incidence
per 100,000 per year
- 2-2.25
- 1.75-2
- 1.5-1.75
- 1.25-1.5
- 1-1.25
- .75-1
- .5-.75

1

2 Figure 4: Map of incidence of dermatitis herpetiformis by regional government office

1 Table 3: Point prevalence of coeliac disease and dermatitis herpetiformis, 30 June 2011

	Coeliac Disease (n)	Prevalence (%)	95% CI	Dermatitis Herpetiformis (n)	Prevalence (%)	95% CI
Overall	10872	0.24	[0.24,0.25]	1160	0.03	[0.02,0.03]
Sex	.	.	.	.	.	.
Male	3662	0.16	[0.16,0.17]	560	0.03	[0.02,0.03]
Female	7210	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	1026	0.15	[0.14,0.16]	64	0.01	[0.01,0.01]
30-49	2952	0.23	[0.22,0.24]	245	0.02	[0.02,0.02]
50-69	3948	0.37	[0.36,0.38]	491	0.05	[0.04,0.05]
70+	1950	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	1267	0.24	[0.22,0.25]	121	0.02	[0.02,0.03]
Yorkshire & 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	1072	0.28	[0.26,0.30]	106	0.03	[0.02,0.03]
South Central	1408	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	1019	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	1203	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]

2

3
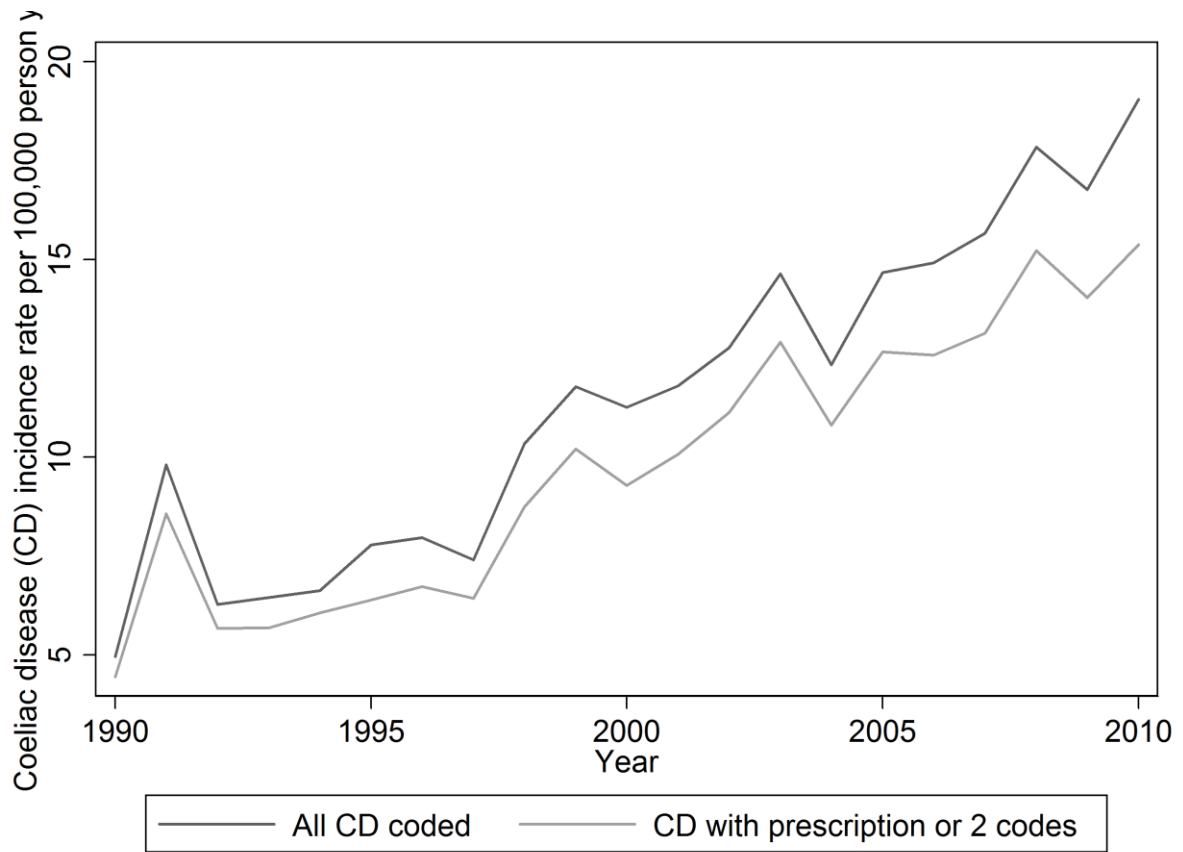
Figure 5: Incidence of coeliac disease (CD) overall, and when the definition is restricted to either 2

3   diagnostic codes or a gluten free prescription.
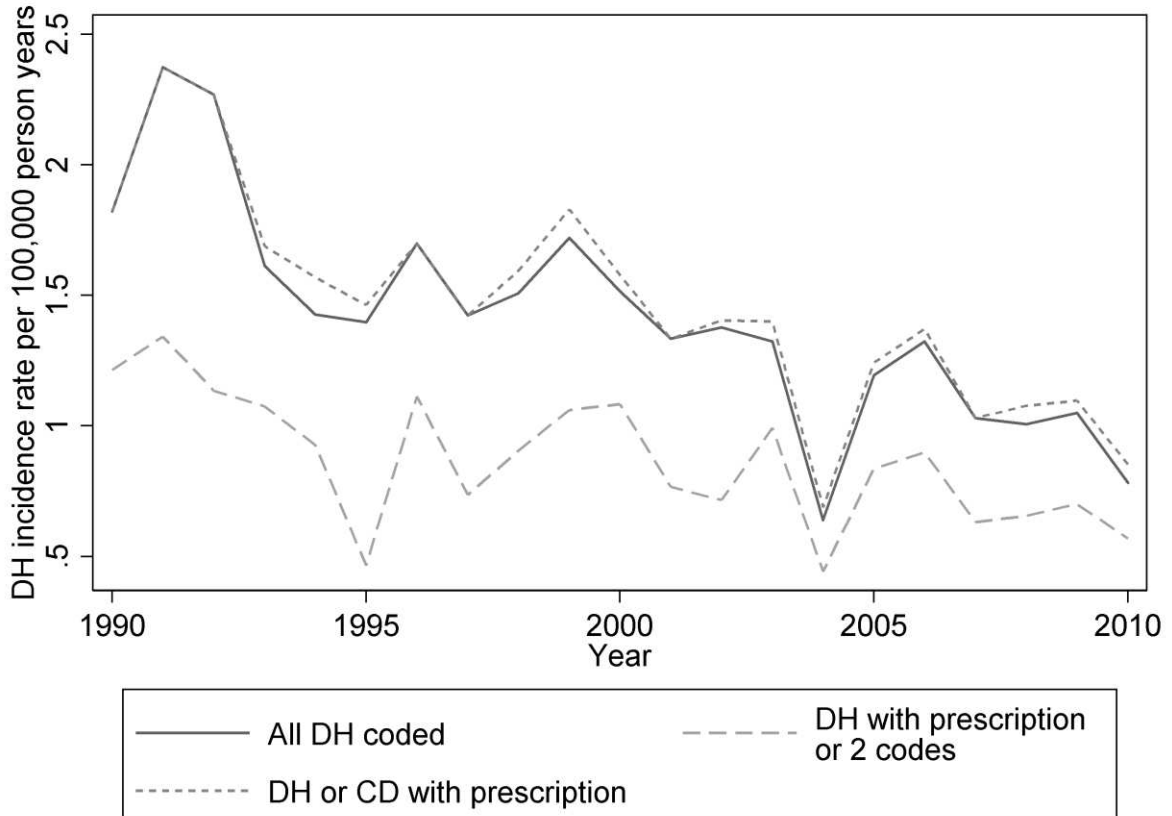
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2 Figure 6: Incidence of dermatitis herpetiformis (DH) overall, the restricted definition to either 2

3 diagnostic codes or a dapsone or gluten free prescription, and the broader definition including

4 coeliac disease patients with a prescription for dapsone.

5

6

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