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Causes of death in people with coeliac disease in England compared with the general population: a competing risk analysis

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ABSTRACT

Introduction Quantifying excess cause-specific mortality among people with coeliac disease (CD) compared with the general population accounting for competing risks will allow accurate information to be given on risk of death from specific causes.

Method We identified from the Clinical Practice Research Datalink all patients with CD linked to Office for National Statistics between 1998 and 2012. We selected controls by frequency matching from the registered general practice population within 10-year age bands. We calculated the adjusted cumulative incidence (including adjustment for competing risks) and excess cumulative incidence for different causes of death up to 10 years from diagnosis.

Results Of the 10 825 patients with CD, 773 died within the study period. The overall mortality rate among patients with CD was 128/10 000 person years compared with 153/10 000 in controls (HR=0.94 95% CI 0.84 to 1.01). We found no overall difference in the cumulative incidence of respiratory disease, digestive disease or cancer related death among cases and controls. The adjusted cumulative incidence of death from cardiovascular deaths was slightly lower compared with those without CD diagnosis (CD 0.32% vs controls 0.41%) with a corresponding excess cumulative incidence of −0.08% (95% CI −0.13 to −0.04). However, patients with CD had 0.15% excess risk (95% CI 0.03 to 0.27) of deaths from non-Hodgkin's lymphoma from the general population baseline risk.

Conclusions Overall, people with CD have no major excess risk of cancer, digestive disease or respiratory disease related or cardiovascular mortality compared with the general population. These findings should be reassuring to patients with CD and clinicians managing their care.

Significance of this study

What is already known on this subject?

- Coeliac disease (CD) affects 1% of the European population yet only approximately 0.2% are clinically diagnosed.
- There is a lack of contemporary knowledge about the causes of death among clinically diagnosed patients which may be useful in determining strategies to reduce some of the associated mortality.
- None of the previous studies on the subject have adjusted their analysis for competing risk which may lead to overestimation of associated cause-specific mortality risks.

What are the new findings?

- By 10 years after diagnosis people with CD have no major excess risk of cancer, digestive disease or respiratory disease related, or cardiovascular mortality compared with the general population.
- Those with CD had a slightly lower cumulative incidence of cardiovascular death following diagnosis.
- Patients with CD had a 0.15% excess risk of dying from non-Hodgkin's lymphoma up to 10 years post diagnosis.

How might it impact on clinical practice in the foreseeable future?

- Our study provides the most contemporary estimates of the risk of cause-specific mortality among patients with CD. Overall our results should be reassuring to patients and practitioners.

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INTRODUCTION

Coeliac disease (CD) affects 1% of the European population yet only approximately 0.2% is clinically diagnosed.[1 2] Numerous population based studies have addressed the overall mortality risk of people with either diagnosed CD or serologically positive disease in the general population and shown widely different findings. For instance, a meta-analysis done on the subject reported estimates ranging from a twofold increase in all-cause mortality among patients with CD compared with the general population to no increase in risk at all.[3] Despite this work, there is a lack of contemporary knowledge about the causes of death among clinically diagnosed patients which, if available, may be useful in determining strategies to reduce some of the associated mortality, if any such increases are shown to exist.

Only a few studies[4–10] have systematically analysed causes of death among people with CD compared with the general population. For instance, small UK based studies from cohorts predominantly diagnosed in the 1980s and 1990s (with less than 200 deaths)[6 9 10] have consistently reported slightly higher cancer and digestive disease (International

Classification of Diseases V.2010 (ICD-10); K00–K93) related mortality but have found no statistically significant increased risk of respiratory disease related or cardiovascular mortality compared with the general population. In contrast, Peters *et al*[7] using Swedish inpatient registry data (from 828 deaths in patients diagnosed between 1965 and 1994) reported statistically significant 1.4-fold, threefold and eightfold increased risks of cardiovascular, respiratory disease and digestive disease related mortality, respectively, compared with the control population. Ludvigsson *et al*[8] conducted the largest study on the subject, also from Sweden, which analysed 3049 deaths of patients diagnosed with CD between 1969 and 2008. Although the study reported a 39% increased risk of all-cause mortality among patients with CD compared with the general population, and excess of 19%, 55% and 36% for cardiovascular, neoplasm and respiratory disease related deaths, respectively, their absolute excess risk was low (0.6, 1.1 and 0.2 per 1000 person years, respectively). Furthermore they also failed to assess whether diagnosis or causes of death had changed over time as their study spanned over 40 years. It is noteworthy that no previous study has adjusted their analysis for competing events (ie, taken into account that patients may die from causes other than those of interest). For instance, if patients with CD are more likely to die from neoplasm, then their risk of death from other causes will be lower which needs to be taken into account. Not adequately adjusting for competing risks may lead to overestimation of cause-specific mortality risks.

In addition, there may be different patterns of morbidity and mortality among the general population and among people with CD between countries in which studies are carried out.[8 9] Finally, there is lack of evidence quantifying the absolute excess risk of specific causes of death compared with the general population. Clearly determining this latter quantity in different countries and healthcare settings is of clinical importance for the purposes of informing patients and clinicians worldwide. Therefore, in this study, using electronic health primary care data linked to national mortality data in England, UK, we have quantified the excess cause-specific mortality among people with CD by 10 years of diagnosis compared with the general population while accounting for competing risks.

METHODS

Data source

We used the Clinical Practice Research Datalink[11] (CPRD) which is a large longitudinal UK database of computerised primary care (ie, general practice) records. The vast majority of the UK population is registered with general practitioners,[12] who are responsible for overseeing a patient's medical care which includes coordination of their healthcare from hospital or other secondary care facilities. The CPRD is subjected to quality checks and a practice's data is only used when it is of high enough quality for research.[13] This is denoted by defining an up-to-standard (UTS) time period for each practice. For the purpose of this study we used the 53% of CPRD practices for which cause-specific mortality data was available from the Office for National Statistics (ONS) death register. The CPRD data linked to ONS is available from 1998 onwards and covers approximately 3% of the English population. As this linkage only covers England, practices from Northern Ireland, Wales and Scotland were excluded. This study was approved by the Independent Scientific Advisory Committee of the CPRD (protocol 12_106R).

Study population

We previously identified people with CD from the general practice data between 1990 and 2012.[1] From this population we then selected the subgroup who were registered with primary care practices that had consented linking to the ONS death registry between 1998 and 2012. The diagnosis of CD was based on Read codes representing CD (J690.00 CD; J690.13 Gluten enteropathy; J690z00 CD NOS; J690100 Acquired CD; J690.14 Sprue-nontropical; J690000 Congenital CD). Patients could have a diagnosis of CD and dermatitis herpetiformis (DH) but not DH alone. Each patient was assigned a date of diagnosis corresponding to the date of their first record of CD.

Comparison group

Controls were selected from the general population who did not have a diagnosis of CD. For the present study controls were only included if they were registered to primary care practices that had consented to linkage with ONS data (the same criteria as for the cases in our study). We also excluded controls with any record of gluten-free prescription or those with DH without CD diagnosis. For this group a random date, 'pseudo diagnosis date' was generated between their date of birth and study end date. We then calculated the age at 'pseudo diagnosis date' for controls and frequency matched them to cases' age at diagnosis in 10-year age bands at a ratio of 10 controls to 1 case.

Follow-up

An open cohort study design was used within which people could enter and exit at different calendar times and ages. The study start date was defined as the latest of: the start of linked data with ONS (1 April 1998), the date of patient registration with the practice and the 'UTS date' of that practice. For the purpose of this study, we included incidence and prevalent CD cases as previously defined.[1] Incident CD cases were followed up from the date of diagnosis rather than their entry date into the database. To sample a comparable follow-up time in the controls, we followed them up from the 'pseudo diagnosis date' rather than their entry date into the database. Failure to do this introduces a bias into the comparison as controls are followed up for a longer time from a younger age than cases. The study end date was defined as the earliest of: the last date for linked primary care data (22 June 2012), the date of patient transfer out from practice, the date of patient's death or the last date of data collection from that practice.

Cause of death

Information on the underlying cause of death was extracted from the ONS death register which records and codes all deaths occurring in England from the death certificates based on WHO guidelines.[14] These define causes of death by ICD-10 codes with the main underlying cause established for each death using standardised rules. For this study we analysed the underlying cause of death by the most frequent ICD-10 chapter headings of neoplasms (ICD chapters C and D), circulatory disease (ICD chapter I: including cerebrovascular and ischaemic heart disease), respiratory disease (ICD chapter J), digestive disease (ICD chapter K) and the remaining less frequent chapter headings grouped together in an 'other causes' category. Causes of death prior to 2001 were coded using ICD-9 and were therefore mapped onto the relevant ICD-10 chapter headings. For our cases and controls, we also used the information on age (at diagnosis date), sex and socioeconomic status (SES, derived from a

patient's area of residence). Areas of residence within England are ranked according to the Indices of Multiple Deprivation which comprise of a number of indicators covering different aspects of deprivation (housing, employment, income, access to services, education and skills, crime, living environment). These ranked scores are then split into quintiles for the purposes of analysis.

Statistical analysis

Crude mortality rates

Initially we calculated crude mortality rates among those with and without CD per 10 000 person years. These rates where then stratified by the most frequent ICD-10 chapter headings. We also analysed specific causes of death under each ICD-10 chapter heading where there were previously published associations with CD.[9]

Adjusted analysis

As previously stated when studying causes of death, the group of survivors (those who do not die during a particular point in time) might not be representative of the initial cohort as deaths from other causes can select out those with relevant risk factors.[15] One method to adjust for this bias uses cumulative incidence functions (CIFs) (ie, the predicted adjusted cumulative risk of death) from a competing risks model that calculates the probability of overall survival from all causes, combined with the instantaneous hazard of death for each specific cause. We calculated CIFs for each specific cause of death using the basic survival functions and HRs from the adjusted Cox proportional hazards model by 10 years from diagnosis of CD. These models were adjusted for age, sex and SES. We calculated the absolute excess risk for each specific cause of death by taking the difference between the CIFs of those with and without CD. The 95% CIs were calculated by bootstrapping (50 iterations). We repeated the above analysis only for those with an incident diagnosis of CD within the CPRD UTS period. Finally, for incident CD cases we identified those who had CD symptoms recorded in the year prior to diagnosis. We only included symptoms of diarrhoea, anaemia and weight loss in this subanalysis, because other associated symptoms of tiredness and abdominal pain/bloating were less specific and susceptible to misclassification. The CIFs and excess risk were then stratified by those with and without having symptoms recorded within a year before diagnosis.

Sensitivity analysis

We increased the specificity of our case definition by repeating our incidence analyses after restricting our case population to those who in addition to one diagnostic code of CD had either; a relevant prescription for a gluten-free product or a second documented record of their disease.

Ethical statement

This study was approved by the Independent Scientific Advisory Committee reference number=10_193R.

RESULTS

Study population

Our cohort consisted of 10 825 patients with CD frequency matched on age to 107 096 people without CD, contributing 60 225 and 640 086 person years of follow-up times, respectively. The median follow-up from the study start to end dates was calculated to be 5 years (IQR=2–10 years). Table 1 presents the basic demographic characteristics of people with and without CD along with the number of deaths which occurred under each ICD-10 chapter heading. For the purpose of this study we grouped together chapter headings as 'other causes' for which we had less than 10 deaths per heading in our CD group which also included the symptoms' chapter. The most frequent chapter heading under 'other causes' was 'infection' followed by 'dermatological'. Compared with those without CD, our CD cases were more likely to be women, slightly older and belonging to higher social class.

Table 1 Basic characteristics of the study population

	Without CD N=107 096		With CD N=10 825	
Characteristics	**No.**	**Per cent**	**No.**	**Per cent**
Cohort (n)				
Deaths	9810	–	773	–
Person years	640 086	–	60 225	–
Median follow-up in years (IQR)	4.7 (1.7–10.1)		4.6 (1.7–9.0)	
Sex (n=patients)				
Male	52 401	48.9	3779	34.9
Female	54 695	51.1	7046	65.1
Age in years* (n=patients)				
<5	5074	4.7	373	3.4
5–17	8631	8.1	1012	9.3
18–29	14 698	13.7	1454	13.4
30–49	35 886	33.5	3599	33.2
50–69	31 093	29	3135	29
>69	11 714	10.9	1252	11.6
SES quintile (n=patients)				
1 (least deprived)	24 644	23.2	2946	27.5
2	24 448	23	2592	24.2
3	20 628	19.4	2111	19.7
4	21 101	19.9	1830	17.1
5 (Most deprived)	15 452	14.5	1253	11.7
Cause of death (n=deaths)				
Circulatory	3244	33.1	209	27
Neoplasm	2763	28.2	229	29.6
Respiratory	1214	12.4	103	13.3
Digestive	438	4.5	52	6.7
Neurological	257	2.6	21	2.7
Genitourinary	177	1.8	16	2.1
Endocrine	120	1.2	15	1.9
Psychiatric	247	2.5	15	1.7
External	211	2.1	13	1.7
Musculoskeletal	69	0.7	10	1.3
Other	344	3.5	27	3.5
Not coded	726	7.4	63	8.2

*Age at diagnosis or start of study follow-up for prevalent CD cases.
CD, coeliac disease; SES, socioeconomic status.

Crude mortality rate

Overall, there were 773 deaths among people with CD and 9810 in those without CD, giving overall mortality rates of 128 and 153 per 10 000 person years, respectively. These rates were not statistically different after adjusting for age and sex (HR=0.94 (95% CI 0.84 to 1.01)). Table 2 shows the mortality rates stratified by ICD-10 chapter headings. Overall the rate of death from neoplasm among those with CD compared with

Table 2 Mortality rates per 10 000 person years stratified by International Classification of Diseases V.2010 (ICD-10) headings

	With CD				Without CD			
Cause of death	n	Rate	95% CI		n	Rate	95% CI	
Overall mortality	773	128	119	137	9810	153	150	156
Neoplasm overall	229	38.0	33.4	43.3	2763	43.2	41.6	44.8
Oesophagus/stomach	21	3.5	2.3	5.3	210	3.3	2.9	3.8
Colon	19	3.2	2.0	4.9	151	2.4	2.0	2.8
Pancreas	19	3.2	2.0	4.9	144	2.2	1.9	2.6
Digestive (other)	16	2.7	1.6	4.3	187	2.9	2.5	3.4
Respiratory	39	6.5	4.7	8.9	604	9.4	8.7	10.2
Skin/bone/breast	14	2.3	1.4	3.9	316	4.9	4.4	5.5
Prostrate	10	1.7	0.9	3.1	212	3.3	2.9	3.8
Non-Hodgkin's lymphoma	26	4.3	2.9	6.3	90	1.4	1.1	1.7
Leukaemia	7	1.2	0.6	2.4	78	1.2	1.0	1.5
Other or benign	58	9.6	7.4	12.5	772	12.1	11.2	12.9
Cardiovascular overall	209	34.7	30.3	39.7	3244	50.7	49.0	52.5
IHD	72	12.0	9.5	15.1	1303	20.4	19.3	21.5
Heart-other	29	4.8	3.3	6.9	512	8.0	7.3	8.7
CVA	81	13.4	10.8	16.7	833	13.0	12.2	13.9
Other-circulatory	27	4.5	3.1	6.5	596	9.3	8.6	10.1
Respiratory overall	103	17.1	14.1	20.7	1214	19.0	17.9	20.1
Respiratory infection	37	6.1	4.5	8.5	439	6.9	6.2	7.5
Chronic airway disease	39	6.5	4.7	8.9	414	6.5	5.9	7.1
Respiratory-other	27	4.5	3.1	6.5	361	5.6	5.1	6.3
Digestive overall	52	8.6	6.6	11.3	438	6.8	6.2	7.5
Upper-GI	2	0.3	0.1	1.3	98	1.5	1.3	1.9
Lower-GI	17	2.8	1.8	4.5	188	2.9	2.5	3.4
Liver/gall bladder/pancreas	22	3.7	2.4	5.5	148	2.3	2.0	2.7
Digestive-other	11	1.8	1.0	3.3	4	0.1	0.0	0.2
Neurological	21	3.5	2.3	5.3	257	4.0	3.6	4.5
Genitourinary	16	2.7	1.6	4.3	177	2.8	2.4	3.2
Endocrine	15	2.5	1.5	4.1	120	1.9	1.6	2.2
Psychiatric	15	2.5	1.5	4.1	247	3.9	3.4	4.4
External	13	2.2	1.3	3.7	211	3.3	2.9	3.8
Other	37	6.1	4.5	8.5	413	6.5	5.9	7.1
Not coded	63	10.5	8.2	13.4	726	11.3	10.5	12.2

CD, coeliac disease; CVA, cerebrovascular accident; IHD, ischaemic heart disease.

those without CD was broadly similar (38 vs 43 per 10 000 person years). However, non-Hodgkin's lymphoma was associated with an absolute excess mortality rate of 3 per 10 000 person years compared with those without CD (absolute rate=4.3 vs 1.4 per 10 000 person years). CD cases had a slightly lower rate of dying from breast, respiratory and prostate cancers (absolute rate=1.3, 6.5 and 0.17 per 10 000 person years, respectively). Patients with CD also had an overall lower rate of death from cardiovascular disease compared with our control population (35 vs 51 per 10 000 person years), but had higher risk of dying from digestive diseases (9 vs 7 per 10 000 person years).

Cumulative incidence function

The above crude comparisons were not adjusted for age or competing risks. We therefore determined the CIF of death for the most frequent causes of death by ICD-10 chapter heading after accounting for competing events (table 3). While the median follow-up for our study was around 5 years, patients could enter and leave the follow-up to contribute their average of 5 years at any point in the subsequent 10 years after CD diagnosis. This open cohort method allowed us to calculate cumulative incidence of death by 10 years after CD diagnosis. The cumulative incidence of cardiovascular death by 10 years post diagnosis was slightly lower for those with CD compared with controls (3.35% vs 4.72%) which corresponded to an excess CI of −1.38% (95% CI −1.91 to −0.85). We observed that those between the ages of 60–79 years had around 3% lower risk of cardiovascular deaths by 10 years after CD diagnosis. Similarly, those over the age of 80 years had 3% lower risk of respiratory disease related deaths whereas those under the age of 50 years had a very slight excess risk (0.18%) of respiratory disease related deaths.

After adjusting cumulative incidence for competing events, sex, SES and age, the overall cumulative incidence of death by 10 years was calculated to be 2% among those with CD (figure 1). We observed that there were no statistically significant differences for the overall cancer, digestive disease or respiratory disease related mortality among those with and without CD (table 4). However, patients with CD had a slightly lower risk of cardiovascular deaths (excess CI −0.08% 95% CI −0.13 to −0.04). Within neoplasm, we found that the cumulative incidence of deaths from non-Hodgkin's lymphoma was higher for our case population corresponding to an excess CI of 0.15%

Table 3 Cumulative incidence function and excess risk by 10 years post coeliac disease (CD) diagnosis adjusting for competing risk. The results are stratified by age at diagnosis

Cause of death	With CD	Without CD	Excess	95% CI*	
Cardiovascular overall (years)	3.35	4.72	−1.38	−1.91	−0.85
≤50	0.38	0.31	0.07	−0.18	0.33
50–59	1.64	1.93	−0.28	−1.05	0.48
60–69	3.55	6.28	−2.73	−4.19	−1.27
70–79	13.14	16.63	−3.49	−6.35	−0.64
≥80	27.99	32.39	−4.40	−10.30	1.51
Respiratory overall (years)	1.55	1.70	−0.15	−0.52	0.21
≤50	0.25	0.07	0.18	0.00	0.35
50–59	0.61	0.57	0.05	−0.53	0.62
60–69	2.19	1.87	0.32	−0.78	1.42
70–79	6.76	6.47	0.29	−2.13	2.71
≥80	9.87	13.13	−3.26	−6.28	−0.25
Neoplasm overall (years)	3.78	4.09	−0.31	−0.87	0.26
≤50	0.88	0.61	0.27	−0.11	0.65
50–59	3.83	3.28	0.55	−0.58	1.68
60–69	7.59	8.04	−0.45	−2.41	1.51
70–79	11.61	12.05	−0.45	−3.25	2.36
≥80	10.31	12.52	−2.22	−6.01	1.57
Digestive overall (years)	0.85	0.65	0.20	−0.07	0.48
≤50	0.37	0.14	0.23	−0.03	0.48
50–59	0.94	0.44	0.50	0.00	0.99
60–69	1.55	0.83	0.73	−0.13	1.58
70–79	1.36	1.82	−0.47	−1.52	0.59
≥80	3.26	3.55	−0.29	−2.93	2.34
Others overall (years)	1.78	2.03	−0.25	−0.62	0.12
≤50	0.46	0.43	0.02	−0.22	0.27
50–59	0.93	0.74	0.20	−0.46	0.86
60–69	1.08	1.65	−0.57	−1.45	0.30
70–79	4.89	5.94	−1.06	−3.11	1.00
≥80	19.30	17.80	1.51	−3.53	6.54
Not coded overall	0.81	0.84	−0.03	−0.28	0.23

*Bootstrap 50 iterations.

(95% CI 0.03 to 0.27). Our cumulative incidence up to 10 years remained fairly similar when we restricted our analysis to only incidence cases and stratified by those with and without symptoms recorded within a year before CD diagnosis (table 5).

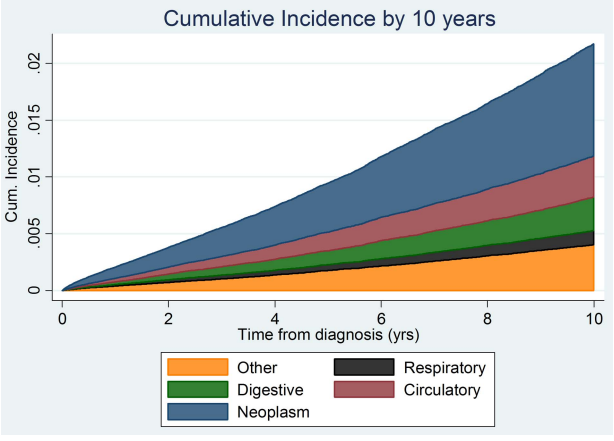

Figure 1 Cumulative incidence by time after diagnosis, adjusting for competing events, age and sex.

Table 4 Cumulative incidence function by 10 years of diagnosis adjusted for competing risk, age, socioeconomic status and gender

Cause of death	With CD	Without CD	Excess	95% CI*	
Cardiovascular	0.32	0.41	−0.08	−0.13	−0.04
Ischemic heart disease	0.15	0.26	−0.05	−0.10	−0.00
Respiratory	0.11	0.10	0.00	−0.02	0.03
Respiratory infection	0.16	0.20	−0.04	−0.09	0.01
Neoplasm	1.24	1.21	0.04	−0.10	0.18
Non-Hodgkin's lymphoma	0.21	0.06	0.15	0.03	0.27
Digestive	0.24	0.16	0.07	−0.01	0.16
Others	0.27	0.29	−0.02	−0.07	0.04
Not coded	0.27	0.25	0.02	−0.07	0.10

*Bootstrap 50 iterations.
CD, coeliac disease.

Sensitivity analysis

Seventy-six per cent of our CD cases received a relevant prescription for a gluten-free product and/or a second documented record of their disease. We found that our overall and cause-specific mortality rates remained unchanged when we applied our restrictive case definition (see online supplementary table S1).

DISCUSSION

Main findings

We have calculated the excess cumulative incidence of death following a diagnosis of CD compared with the general

Table 5 Cumulative incidence function (CIF) by 10 years of diagnosis adjusted for competing risk, age, socioeconomic status and gender

Cause of death	Deaths n	CIF with CD	Excess*	95% CI†	
Restricting to only incident cases (overall CD cases=4687)					
Cardiovascular	72	0.27	−0.13	−0.19	−0.07
Respiratory	30	0.07	−0.02	−0.05	0.01
Neoplasm	86	1.12	−0.05	−0.33	0.22
Digestive	18	0.19	0.04	−0.04	0.13
Others	38	0.22	−0.06	−0.14	0.01
Not coded	27	0.30	0.04	−0.09	0.17
Restricting to symptomatic incident cases (overall CD cases=1895)					
Cardiovascular	34	0.25	−0.16	−0.24	−0.07
Respiratory	16	0.08	−0.02	−0.06	0.01
Neoplasm	36	0.97	−0.20	−0.51	0.12
Digestive	7	0.15	0.00	−0.08	0.09
Others	15	0.17	−0.11	−0.19	−0.03
Not coded	13	0.29	0.04	−0.11	0.18
Restricting to non-symptomatic incident cases (overall CD cases=2792)					
Cardiovascular	38	0.29	−0.11	−0.20	−0.01
Respiratory	14	0.07	−0.02	−0.07	0.03
Neoplasm	50	1.25	0.09	−0.30	0.47
Digestive	11	0.22	0.08	−0.05	0.20
Others	23	0.28	−0.01	−0.13	0.10
Not coded	14	0.30	0.04	−0.13	0.22

The results are restricted to the incident cases and stratified by whether or not symptoms were recorded within a year before diagnosis.
*Excess risk compared with controls.
†Bootstrap 50 iterations.
CD, coeliac disease.

population. We have done this in a large unselected cohort of more than 10 000 patients with CD and assessed the underlying cause while accounting for competing events. Our analysis showed no overall excess risk of cancer, digestive disease or respiratory disease related, or cardiovascular mortality after adjusting for age and sex. In fact, those with CD had a slightly lower cumulative incidence of cardiovascular death following diagnosis. Finally, we observed that patients with CD had a 0.15% excess risk of dying from non-Hodgkin's lymphoma up to 10 years post diagnosis.

Strengths and limitations

Our study used information on more than 10 000 patients with CD diagnosis to analyse excess cumulative incidence of cause-specific deaths compared with those without CD in England. The use of this contemporary, nationally representative primary care data makes our study findings generalisable to patients with clinically diagnosed CD in the UK and allows comparisons with the only other similar data available on this subject, which comes from Sweden.[7 8] Furthermore, we had a large sample size and prospective follow-up, and were able to adjust for competing events which allowed us to calculate accurate, unbiased and more detailed cause-specific cumulative mortality rates than most previous studies done on the subject.

A potential weakness of conducting epidemiological studies using routinely collected data is the validity of the diagnostic data for each patient. However, the diagnosis of CD has been validated in these data with a positive predictive value ranging between 81% and 100%.[16] We found that our cause-specific absolute mortality rates remained unchanged when we restricted our analysis to CD cases who had either a gluten-free prescription or more than one CD diagnostic code in their medical records. Previous studies suggest that of the 1% of the general population that have a positive serology for CD only about 0.2% are clinically diagnosed in the UK.[1 17 18] Therefore it is possible that there may be people with undiagnosed CD in our comparison cohort and it may be argued that we failed to observe excess cause-specific mortality because of the undetected CD in our control population. We believe that the impact of this limitation will however be minimal as a previous study by our group[19] found no difference in the overall and cause-specific mortality among those with undetected CD compared with the general population in England. We acknowledge that our comparison group may include some patients with IBS. However it is very unlikely that this would influence our estimates given that there is no evidence that IBS is associated with increased mortality risk. In our study we found that 6% of our comparison group had a diagnosis of IBS,[20] however, our mortality data remained unaltered when we excluded those patients from our analysis.

Cause of death information in our study was from the ONS death register which uses standardised WHO guidelines to extract information on cause of death from the death certificates. It is important to note that death certificates may be imprecise, yet they are the official legal requirement for ascertaining the cause of death. As a consequence, death certificates are the only standard method to extract information on the cause of death across such a large population as we have used. For the purpose of this study we only used the underlying cause of death information to avoid changes in the coding requirements over time.

Our study also lacked compliance data on a gluten-free diet among those with CD. Corrao *et al*[4] previously demonstrated higher overall mortality among those who were less adherent to a gluten-free diet compared with those who were more adherent. However their study only included a selected group of patents identified from hospital and therefore results may not be generalisable. While our study is one of the largest to look at the mortality among patients with celiac disease, our median follow-up was only 5 years (IQR=1.7–10). Therefore we acknowledge that we may not have been able to capture the very long-term consequences of the disease.

Other studies

We have conducted the first study which has looked at the excess risk of cause-specific death among people with CD while taking into account competing risks. Although there are no other reports available that have carried out such an analysis our overall and cause-specific mortality rates are in concordance with the most contemporary evidence on the subject. For instance, we found neoplasm to be the most common cause of death among patients with CD followed by cardiovascular disease which is broadly consistent with other population based studies from the UK.[6 9]

Overall, we found no excess risk of neoplasm related mortality among patients with CD, a finding which contradicts the conclusion of most previous studies.[6–9 21] For instance, the largest study by Ludvigsson *et al*[8] reported a 55% relative increased risk of neoplasm related deaths among patients with CD compared with controls which is in line with other UK based studies by Grainge *et al*[9] and Solaymani-Dodaran *et al*.[6] This may be due to the fact that the previous studies did not adjust for the risk of dying from other causes or that the Swedish data had a far greater proportion of children in it than ours and the Lothian and Derby studies had cohorts which were mainly diagnosed before the year 2000. The unadjusted estimates handle death from other causes as censoring which assumes that the risk of death for the people who die is the same as for the people who did not die. In most scenarios this does not make biological sense.[22] Furthermore, not adequately adjusting for competing risk of death can result in considerable overestimation (depending on the duration of follow-up) of cause-specific death rates which can give misleading results when comparing the occurrence of an outcome of interest. After adjusting for competing risks, we did identify a statistically significant excess risk of death from non-Hodgkin's lymphoma (<0.1%) which is consistent with other studies.[4–7 9]

We observed a slightly lower risk of cardiovascular deaths among those with CD. This finding is supported by another population based study by West *et al*[23] who reported a lower prevalence of hypertension and hypercholesterolaemia compared with the general population using the same database. Our study showed no statistically significant excessive risk of non-malignant digestive disease or respiratory disease related deaths among patients with CD. In contrast, a previous study from Sweden[8] reported a 36% increased risk of respiratory disease related mortality. Finally, Grainge *et al*[9] reported a fourfold increased risk of non-malignant digestive disease related deaths among patients with CD. However their results were based on few cases (n=10) giving a wide CI. Moreover, the likelihood of detecting CD may increase during the investigation for other digestive diseases, therefore the excess risk of digestive disease related mortality observed in the previous study may be attributable to more detailed investigations being carried out among those patients, that is, an ascertainment bias phenomenon.

Implications

Our study has demonstrated that patients with CD have no major excessive risk of cancer, digestive disease or respiratory disease related, or cardiovascular mortality compared with the general population. There is an excess risk of dying of non-Hodgkin's lymphoma among patients with CD but the excess cumulative risk is very small indeed. Overall our findings are reassuring to patients with CD and clinicians managing their care.

Contributors AAS and JW conceived the idea for the study, with KMF, CJC, TC and LJT also making important contributions to the design of the study. AAS carried out the data management and analysis and wrote the first draft of the manuscript. All authors were involved in the interpretation of the data, contributed towards critical revision of the manuscript and approved the final draft. AAS had full access to all of the data and final responsibility for the decision to submit for publication.

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