This is the accepted manuscript of the article, which has been published in
American journal of gastroenterology, 2020, 115:7, 1117-1124.
http://dx.doi.org/10.14309/ajg.0000000000000665

Overall and cause-specific mortality in adult celiac disease and dermatitis herpetiformis diagnosed in the 21st century

Inka Koskinen, MD[1,2], Lauri J Virta, MD, PhD[3], Heini Huhtala, MSc[4], Tuire Ilus, MD, PhD[1,5], Katri Kaukinen, MD, PhD[1,6] and Pekka Collin, MD, PhD[1,5]

[1]Celiac Disease Research Center, Faculty of Medicine and Health Technology, Tampere University, Finland

[2]Department of Internal Medicine, Central Finland Central Hospital, Jyväskylä, Finland

[3]Research Department, Social Insurance Institution of Finland, Turku, Finland

[4]Faculty of Social Sciences, Tampere University, Finland

[5]Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland

[6]Department of Internal Medicine, Tampere University Hospital, Tampere, Finland

Corresponding author: Katri Kaukinen, MD, PhD. E-mail: katri.kaukinen@tuni.fi

Word count: 2965

Conflicts of interest

Guarantor of the article: Katri Kaukinen, MD, PhD

Specific author contributions: Inka Koskinen: study design, project coordination, data collection, data interpretation and writing the article; Lauri J. Virta: study design, data collection, data interpretation and manuscript revision; Heini Huhtala: data analysis and manuscript revision ; Tuire Ilus: study design and manuscript revision; Katri Kaukinen: study design, data interpretation and manuscript revision; Pekka Collin: study design, data interpretation and manuscript revision . All authors have read and approved the final manuscript.

Financial support: This work was supported by grants to the Celiac Disease Study Group from the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (Grant 9P060)

Potential competing interest: None

Running head: Mortality in celiac disease

Keywords: celiac disease, adult, 21st century, recent diagnostic advances, mortality

Study Highlights

1. WHAT IS KNOWN

- Celiac disease has been associated with increased mortality, but the data are contradictory.
- Celiac disease patients have an increased risk of dying from lymphoproliferative diseases and gastrointestinal malignancies.

2. WHAT IS NEW HERE

- Overall mortality was not increased in a contemporary, large, and nationwide Finnish cohort of celiac patients diagnosed in adulthood.
- Mortality from lymphoproliferative diseases was elevated, but lower than previously reported.
- Mortality from gastrointestinal malignancies was not increased.
- Hazard ratios for death from non-malignant digestive diseases and lymphoproliferative diseases peaked within two years of the celiac disease diagnosis.

Abstract

Objectives: We assessed whether celiac disease-associated mortality is increased among patients diagnosed in the 21st century given recent improvements in diagnostic and treatment facilities.

Methods: Biopsy-proven celiac disease (Marsh III) and dermatitis herpetiformis patients aged 20–79 years (median 50 years) diagnosed 2005 – 2014 (n=12,803) were identified from the national dietary grant registry. Dates and causes of death were obtained from Statistics Finland. Overall mortality and causes of death were compared to reference individuals (n=38,384) matched for age, sex, and area of residence (at the time of celiac disease diagnosis) selected from the Population Information System.

Results: During a mean follow-up of 7.7 years (SD ± 3.0 years), 884 (6.9%) and 2,613 (6.8%) deaths occurred among the celiac cohort and reference group respectively. Overall mortality (hazard ratio (HR) 1.01, 95% confidence intervals (CI) 0.94–1.09), mortality from all malignancies (HR 1.11, 95% CI 0.96-1.27), gastrointestinal tract malignancies (HR 1.21, 95% CI 0.56-1.71) or cardiovascular diseases (HR 0.91, 95% CI 0.77-1.07) were not increased among celiac patients. Overall, mortality from lymphoproliferative diseases (HR 2.36, 95% CI 1.65–3.39) and non-malignant digestive diseases (HR 2.19, 95% CI 1.40–3.43) was increased, but HRs decreased after exclusion of the first two years of follow-up (HR 1.71, 95% CI 1.10–2.66 and HR 1.75, 95% CI 1.01–3.05 respectively).

Conclusions: The overall mortality in adult celiac disease diagnosed 2005-2014 was not increased. Mortality from lymphoproliferative diseases was increased but lower than previously reported.

Introduction

Recent studies indicate that the prevalence of celiac disease, a dietary gluten-triggered autoimmune-mediated enteropathy, is increasing, affecting 1–2% of the population globally (1-5). Nevertheless, the disease remains markedly under-diagnosed (1,6-8). Along with the classical symptoms of diarrhea and malabsorption, celiac disease may manifest with mild abdominal or extraintestinal symptoms, or there may be no symptoms whatsoever. With a strict gluten-free diet, it is possible to heal the damaged small bowel mucosa (9) and to alleviate the symptoms.

Celiac disease has been associated with increased mortality mainly caused by lymphoproliferative diseases and diseases of the gastrointestinal organs (10-13). Most publications have concerned tertiary center or hospital-based cohorts of celiac patients diagnosed mainly before the advent of serological testing in the 1980s (10,14-16); at that time celiac disease was commonly diagnosed in childhood with malabsorption, diagnostic delay was prolonged, and facilities for successful treatment were limited. As malabsorption and long diagnostic delay have been associated with complicated celiac disease, these factors may have caused overestimation of mortality. (17,18). A recent study from Nottingham in the UK utilizing general practice data from the 2000s suggested an improved prognosis for celiac patients; the relative mortality risk paralleled that of the general population (19).

In Finland, health personnel have been educated about celiac disease and active case-finding has been advocated by screening individuals presenting with mild symptoms or belonging to known celiac disease risk groups since the 1990s (20). This approach has yielded a globally high prevalence (0.7%) of biopsy-proven celiac disease (7,20,21) and a shortened delay from presenting symptoms to diagnosis (15,22-24). Simultaneously, awareness of celiac disease has increased and

legislation is in place to ensure the quality of currently widely available gluten-free products. Newly diagnosed patients are referred to dieticians and, according to dietary interview studies, Finnish celiac patients are highly adherent to strict gluten-free diet (25,26) also achieving villous recovery (9). Refractory celiac disease unresponsive to strict gluten-free diet carries a high risk of complications, affects only 0.3% of all adult celiac patients in Finland and is thus expected to have little impact on mortality (7).

Overall, earlier research shows contradictory and decidedly scarce results for celiac disease-associated mortality in contemporary cohorts of patients. Using an unselected nationwide population-based cohort of adult celiac patients diagnosed in the 21st century and assembled from the Finnish dietary reimbursement registry, we explored whether improved diagnostics and treatment have jointly reduced excess mortality risk.

Materials and methods

Study population

From October 2002 to the end of 2015, all Finnish non-institutionalized celiac disease or dermatitis herpetiformis patients were entitled to a monthly dietary reimbursement of 21 euros to cover the additional costs of maintaining a gluten-free diet. Eligibility for reimbursement was based on histological verification of the diagnosis demonstrated by duodenal villous atrophy with crypt hyperplasia (compatible with Marsh III (27)) in celiac disease or typical granular IgA deposits in the dermal papillae of the skin in dermatitis herpetiformis (28).

All applicants for the dietary grant for celiac disease were recorded in a nationwide registry maintained by the Social Insurance Institution of Finland (SII). Before granting the reimbursement, the attainment of the diagnostic criteria was verified by a SII reviewer checking the medical certificate delivered by the treating physician at the time of diagnosis. Reimbursement payments began in the month immediately following the diagnosis (maximum 12 months retrospectively after receiving the application).The validity of the registry has been shown to be excellent (20,21,29). However, only one diagnostic code per patient (K90 for celiac disease or L13 for dermatitis herpetiformis) was accepted thus patients presenting with both manifestations may have been registered under either code. From 2002 to 2004 altogether 21,405 patients joined the registry including those with a prior diagnosis (20). By the end of 2014 the registry included 34,252 patients. Of the reimbursement decisions, 97% were based on code K90 and 3% on code L13 (8).

Retrieval of the patient cohort has been described in detail elsewhere (8). For this study, incident celiac disease and dermatitis herpetiformis – patients aged 20 – 79 years with known time of diagnosis were selected from the dietary grant registry. To ensure that incident cases only were included, only patients entered in the registry between 2005 and 2014 were enrolled. Additionally, registry data prior to 2005 was checked and patients previously granted reimbursement excluded (8). Of the 12,847 celiac patients identified, 36 had set a disclosure prohibition preventing the retrieval of vital details and eight were resident abroad at the time of diagnosis and therefore excluded. Thus, the study population comprised 12,803 celiac patients. The preceding month and year when the dietary grant payments began were used as proxies for the date of diagnosis.

Reference group

For each incident celiac patient, up to three eligible reference individuals matched for age, sex, and place of residence at diagnosis of the corresponding celiac disease cases were selected from the Finnish Population Information System comprising 38,384 individuals. The Population Information System maintained by the Population Register Centre contains basic information on all Finnish and foreign citizens permanently resident in Finland; each individual registered in the system has a unique personal identification code.

Mortality data

Statistics Finland maintains the registry of causes of death covering more than 99% of all deceased residents of Finland since 1936 (30). Immediate, underlying, and contributary causes of death are derived from the death certificates (30). The personal identification codes of both cohorts were linked with the registry. Dates of death were acquired until the end of 2017 and causes of death until the end of 2016. The registry classifies the causes of death by underlying cause into 54 groups (31). These were used in the analyses of cause-specific mortality. Main categories in analyses (according to the codes of the Tenth Revision of the International Classification of Diseases (ICD-10)) included: All malignancies (C00–C97), gastrointestinal tract malignancies covering cancers from esophagus to anus (C15–C21), lymphoproliferative diseases (C81-C96) including all disease locations, cardiovascular diseases (I00–I425, I427–I99), respiratory diseases (J00–J64, J66–J99), and non-malignant digestive diseases (K00–K291, K293–K67, K71–K851, K853–859, K861–K93) covering diseases of liver, pancreas, and gastrointestinal tract (excluding all alcohol-related diseases). Non-Hodgkins lymphomas (C82–C85) and T-cell non-Hodgkins lymphomas (C84) were specifically collected from the mortality data.

Concomitant conditions

Information on concomitant chronic conditions based on granted drug reimbursements was collected from the Special Reimbursement Registry for medicine expences maintained by the SII. Specific conditions taken into consideration (Supplementary Table 1) included insulin dependent diabetes mellitus, hypertension, cardiovascular diseases (including cardiac insufficiency, ischemic heart disease, chronic arrhythmias, and hyperlipidemic diseases), respiratory diseases (including bronchial asthma and chronic obstructive pulmonary disease), and inflammatory rheumatic diseases.

Statistical analyses

The follow-up commenced from the month the diagnosis was set for celiac patients and a corresponding date for reference individuals and continued until death, emigration or December 31st, 2017, whichever occurred first. Crude mortality rates per 10,000 person-years were calculated for overall mortality and for the main categories of causes of death and causes of special interest according to the literature. Cox proportional hazards model was used to calculate hazard ratios (HR) with 95% confidence intervals (CI). Analyses were further adjusted for concomitant conditions. Overall mortality and deaths caused by non-malignant digestive diseases, all malignancies, lymphoproliferative diseases, and gastrointestinal tract malignancies were analyzed separately for two different periods of follow-up; the peri-diagnostic period (<2 years after diagnosis) and the post-diagnostic period (≥2 years after diagnosis). A stratified analysis according to sex and age at diagnosis (20–29, 30–39, 40–49, 50–59, 60–69, 70–79 years) was conducted for overall mortality and lymphoproliferative diseases. Celiac disease-associated mortality in lower and higher incidence areas (32.4 and 48.5/100,000 persons/year respectively) within Finland (20) was also assessed. To determine how mortality from diseases other than malignancies, lymphoproliferative diseases, gastrointestinal malignancies, cardiovascular diseases, ischemic heart diseases, cerebrovascular diseases, respiratory diseases, and digestive diseases individually affected the main results, a

competing risks analysis was performed. The analysis was based on Fine and Gray's proportional sub-hazards model. Analyses were run using SPSS (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY) and STATA (StataCorp, Version 13.0, LP, TX).

Ethics

Data permits were granted by the SII, the Population Register Centre and Statistics Finland. According to Finnish legislation, no informed consent or approval by an ethics committee is required for registry-based studies where study subjects are not contacted.

Results

The basic characteristics are presented in Table 1. The 51,187 adults included in the study yielded a total of 394,988 person-years of follow-up; 99,094 for celiac patients and 295,894 for the reference individuals. Median age at celiac disease diagnosis was 50 years, and mean follow-up was 7.7 years (SD ± 3.0 years). Overall, 884 (6.9%) celiac patients and 2,613 (6.8%) reference individuals died. Overall mortality rate per 10,000 person-years was 89.2 (95% CI 83.5–95.3) in the celiac cohort and 88.3 (95% CI 85.0–91.8) in the reference group. After adjusting for concomitant conditions, the results remained the same. No competing risks were observed.

Table 2 presents the rates for cause-specific mortality. The most frequent causes of death for both groups were malignant neoplasms followed by cardiovascular diseases, particularly ischemic heart disease. Celiac patients had an increased risk of dying from lymphoproliferative diseases (HR 2.36, 95% CI 1.65–3.39), non-malignant digestive diseases (HR 2.19, 95% CI 1.40–3.43), and infections (HR 5.00, 95% CI 1.81-13.69). The HRs for lymphoproliferative and digestive diseases diminished but remained elevated even after exclusion of the first two years of follow-up (Table 3). Moreover, mortality from non-Hodgkins lymphomas was increased in the celiac cohort (HR 4.53, 95% CI

2.84-7.24), and 55% of deaths were caused by T-cell non-Hodgkins lymphomas in the celiac cohort compared to 3% in the reference group. Causes of death from non-malignant digestive diseases among the celiac cohort varied; 7 volvulus, 7 liver cirrhosis (2 primary biliary cholangitis, 5 unspecified), 5 celiac disease, 3 acute intestinal vascular diseases, and 2 gastrointestinal bleedings. Furthermore, stomach ulcer, chronic gastritis, unspecified intestinal occlusion, diverticulosis, intestinal perforation, acute pancreatitis, bile duct stricture, gallbladder perforation, and cholangitis were the cause in one case each. Sepsis was the most frequent infectious underlying cause of death leading to increased mortality among celiac patients (HR 7.44, 95% CI 1.44-38.35). In a post hoc analysis assessing sepsis as both immediate and underlying cause of death, mortality was not increased (HR 1.12, 95% CI 0.68-1.85). Likewise, mortality from pneumococcal infections was not significantly increased (HR 4.47, 95% CI 0.75-26.76). No deaths were due to Hemophilus influenzae or Neisseria meningitidis.

In stratified analyses, no significant differences in overall mortality were detected between the six diagnostic age groups, males (HR 0.98, 95% CI 0.88–1.08), and females (HR 1.05, 95% CI 0.94–1.17) or lower (HR 0.80, 95% CI 0.85–1.13) and higher (HR 1.08, 95% CI 0.94–1.24) incidence areas. Regarding lymphoproliferative diseases, mortality was significantly increased among celiac patients aged 50-69 years (Figure 1). Females had a greater risk (HR 3.77, 95% CI 2.18-6.52) of death from lymphoproliferative diseases than males (HR 1.63, 95% CI 0.99-2.68) in comparison to their own reference individuals.

Discussion

In this large nationwide population-based study, overall mortality was not increased in adult celiac disease diagnosed in the 21st century. This conflicts with the elevated mortality rates reported in

studies on patient cohorts diagnosed earlier (Table 4). A British study on adult celiac patients diagnosed within the same timespan as ours reported comparable results (19).

Changes in celiac disease presentation over time provide a plausible explanation for our results; the proportion of patients presenting with classical phenotype has halved since the 1980s and patients are increasingly diagnosed for mild symptoms or by screening (14,15). Corrao et al. (17) showed an increased mortality in association with classical malabsorptive celiac disease (SMR 2.5), while no excess risk (SMR 1.1) was detected with atypical or screen-detected phenotypes. Indeed, in most studies examining screen-detected celiac disease, mortality was not increased (32-34). By contrast, screen-detected patients had increased mortality (2.5-3.9) in two studies (35,36), but imperfections of the screening-test used in one and small number of cases in the other study may have affected the results. Supporting the assumption that milder celiac disease expression and lower mortality rates are connected, a recent study from Derby in the UK (11) reported a declining trend in excess mortality between patients diagnosed before and after the second millennium, although the elevated risk persisted (SMR 1.6). Likewise, in a Swedish study (12) mortality among celiac patients diagnosed in the 2000s was slightly higher than ours (HR 1.2). The higher prevalence of diagnosed celiac disease in Finland (0.7 compared to 0.2 in Sweden) (1,6,37) offers one explanation for the discrepancy by suggesting that our cohort may contain more patients with mild symptoms. Notably, a lower mortality risk has been associated with dermatitis herpetiformis compared to celiac disease (38). As only 3% of patients in our study had dermatitis herpetiformis and presumably 80% of them also had villous atrophy (39), the effect of pure dermatitis herpetiformis on mortality is negligible.

In contrast to many other studies, we found no excess mortality from all malignancies. Two studies from the UK and two from Sweden with most patients diagnosed before 2000 noted a 60 – 80%

elevated mortality from all malignancies (10,12,40,41), whereas another British study with more recently diagnosed celiac patients reported no elevated risk (19). The celiac patients' absolute risk of dying from lymphoproliferative diseases was relatively low in our study despite the increased relative risk~~. Altogether, the rise was lower than p~~previously reported (Table 4). Mortality from gastrointestinal cancers was not increased, which concurs with the results from the UK (42). Interestingly, despite the decreased incidence of breast cancer in celiac disease (13,29,43), mortality was not significantly reduced. This finding is similar with other recent reports (11,42).

Our finding of elevated mortality from non-malignant digestive diseases was within the range (2- to 8-fold) reported by others (10,11,17,41). Even though celiac disease was an uncommon underlying cause of death in our study constituting 15% of deaths due to digestive diseases, it may still have influenced in additional cases as a contributary factor. Also, the rarity of refractory celiac disease in Finland (7) offers one potential explanation for the low mortality. Celiac disease was the cause in 73% of deaths in an Italian study (17), where the high proportion of patients with either severe disease or lapses in maintaining gluten-free diet could explain the result. Autoimmune liver diseases and cryptogenic liver function abnormalities have been associated with celiac disease and may explain the excess liver mortality (44). The absolute number of volvuli among celiac patients was small and the excess mortality could be coincidental. However, some case reports suggesting an association between volvulus and celiac disease do exist (45).

Celiac disease has been associated with severe infections, especially those due to encapsulated bacteria (mainly pneumococcus) (46,47). Inter alia, hyposplenism and increased mucosal permeability have been hypothesized as predisposing factors (46). Although mortality from sepsis

was increased in our study and resembled the findings reported by Peters et al. (10), the result was based on very few cases. The clinical significance of the finding is obscure, especially considering that the increased risk disappeared when observing both immediate and underlying causes of death. Holmes et al. (11) noted increased mortality from pneumonias and suggested an association with pneumococcal infections. However, only five deaths from pneumococcal infections (2 sepsis and 1 pneumonia in the celiac group and 1 sepsis and 1 pneumonia among the reference group) occurred in our study. These findings suggest that celiac patients diagnosed in the 21st century with milder symptoms and shortened diagnostic delay, have a fairly good prognosis concerning infections.

Mortality from all malignancies, lymphoproliferative diseases, gastrointestinal tract malignancies and digestive diseases was increased in the peri-diagnostic period and declined over time, while overall mortality remained unchanged. Similar findings have been reported elsewhere (12,17,41,48,49). The decline could be explained by ascertainment bias; a fatal disease may be found while conducting examinations for symptoms caused by celiac disease or vice versa.

The major strength of our study is the large and comprehensive population-based sample of biopsy-verified celiac patients diagnosed recently in a country where the proportion of clinically diagnosed celiac disease is high and the whole spectrum of celiac disease phenotypes is covered. As the dietary grant was a tax-free monthly subsidy with no restrictions on its use, presumably nearly all eligible patients applied for it. Furthermore, a group of individually matched reference individuals was used for comparison and, in consideration of the ascertainment bias, the follow-up was divided into peri- and post-diagnostic periods.

Our study also has some limitations. We had no data on patient-specific risk factors including symptom severity and celiac disease phenotype. However, a trend towards milder clinical presentation has been observed in Finland too (16,22,25). These changes in celiac disease presentation could explain our findings. We could not assess patients' adherence to gluten-free diet, but in light of earlier studies among Finnish celiac patients compliance was presumably good (25,26). We may have overestimated adherence, but in that case, mortality would likely be higher. The data on concomitant diseases were derived from drug reimbursement decisions. It is possible that not all patients applied for these, but it is unlikely that celiac patients would have applied for drug reimbursements differently from Finnish people in general. We acknowledge the possibility of inaccuracies in death certificates and imperfections in diagnostics, but this source of bias would likely concern both cases and reference individuals equally.

Conclusions

In conclusion, adult celiac patients diagnosed between 2005 and 2014 had no excess overall mortality, but mortality from lymphoproliferative diseases and non-malignant digestive diseases was increased. Altogether, celiac disease diagnosed in the 21st century seems to have a good prognosis, but further research is needed to ascertain prognostic risk factors since some patients still have a more pessimistic outcome.

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Table 1. Baseline characteristics of the study groups.

Characteristics	Celiac patients n=12,803		Reference individuals n=38,384	
	n	%	n	%
Gender				
Male	4,860	38.0	14,573	38.0
Female	7,943	62.0	23,811	62.0
Age at diagnosis, years				
20–29	1,629	12.7	4,895	12.7
30–39	2,072	16.2	6,199	16.2
40–49	2,589	20.2	7,761	20.2
50–59	2,868	22.4	8,592	22.4
60–69	2,288	17.9	6,867	17.9
70–79	1,357	10.6	4,070	10.6
Concomitant diseases [a]				
Diabetes mellitus	1,303	10.2	3,744	9.8
Hypertension	1,524	11.9	5,208	13.6
Cardiovascular diseases	1,119	8.7	3,052	8.0
Respiratory diseases	1,209	9.4	3,154	8.2
Inflammatory rheumatic diseases	528	4.1	1,354	3.5

[a] Proportion of patients on long term medication according to drug reimbursement decisions

Table 2. Mortality rates per 10,000 person-years and hazard ratios (HR) for overall and cause-specific mortality among celiac patients and their reference individuals.

Cause of death (end of year 2016)	ICD-10 codes	Celiac group (n=12,803)			Reference group (n=38,384)			HR (95% CI)	
		n	(% of deaths)	Mortality rate [a]	n	(% of deaths)	Mortality rate [a]		
Overall mortality [b]		884		89.2	2,613		88.3	1.01	(0.94–1.09)
Malignancies	C00–C97	261	(33.6)	29.0	705	(30.8)	26.2	1.11	(0.96–1.27)
Gastrointestinal tract [c]	C15–C21	49	(5.4)	5.0	114	(4.2)	4.1	1.28	(0.92–1.79)
Esophagus	C15	4	(0.5)	0.4	12	(0.5)	0.5	1.00	(0.32–3.10)
Stomach	C16	8	(1.0)	0.9	20	(0.9)	0.7	1.20	(0.53–2.71)
Small bowel	C17	4	(0.5)	0.4	3	(0.1)	0.1	3.99	(0.89–17.81)
Colorectum [d]	C18–C20	31	(4.0)	3.4	78	(3.4)	2.9	1.19	(0.78–1.80)
Liver	C22	12	(1.5)	1.3	30	(1.3)	1.1	1.19	(0.61–2.33)
Pancreas	C25	26	(3.4)	2.8	64	(2.8)	2.4	1.21	(0.77–1.91)
Lymphoproliferative	C81–C96	53	(6.8)	5.9	67	(2.9)	2.5	**2.36**	**(1.65–3.39)**
NHL	C82–C85	44	(5.6)	4.9	29	(1.2)	1.1	**4.53**	**(2.84–7.24)**
T-cell NHL	C84	24	(3.1)	2.7	1	(0.0)	0.0	**71.67**	**(9.70–529.77)**
Breast [e]	C50	15	(1.9)	1.7	75	(3.3)	2.8	0.60	(0.34–1.04)
Gynecological [e]	C51–C58	12	(1.5)	2.1	42	(1.8)	2.5	0.85	(0.45–1.62)
Prostate [f]	C61	9	(1.2)	2.7	38	(1.7)	3.8	0.71	(0.34–1.46)
Urinary tract	C64–C68	11	(1.4)	1.2	34	(1.5)	1.3	0.97	(049–1.91)
Digestive diseases	K00–K291, K293–K67, K71–K851, K853–859, K861–K93	33	(4.3)	3.7	45	(2.0)	1.7	**2.19**	**(1.40–3.43)**
Liver cirrhosis	K74	7	(0.9)	0.8	5	(0.0)	0.2	**4.18**	**(1.33–13.17)**
Celiac disease	K90	5	(0.6)	0.6	0	(0.0)	0.0		-
Volvulus	K562	7	(0.9)	0.8	2	(0.1)	0.1	**10.48**	**(2.18-50.44)**
Cardiovascular diseases	I00–I425, I427–I99	183	(23.6)	20.3	603	(26.4)	22.4	0.91	(0.77–1.07)
Ischemic heart disease	I20–I25	134	(17.3)	14.9	437	(19.1)	16.2	0.92	(0.76–1.11)
Cerebrovascular disease	I60–I69	46	(5.9)	5.1	176	(7.7)	6.5	0.78	(0.56–1.08)
Respiratory diseases	J00–J64, J66–J99	36	(4.6)	4.0	104	(4.5)	3.9	1.03	(0.71–1.51)
Infectious diseases	A00-B99, J65	10	(1.3)	0.1	6	(0.3)	0.2	**5.00**	**(1.81-13.69)**
Sepsis	A40-A41	5	(0.6)	0.6	2	(0.1)	0.1	**7.44**	**(1.44-38.34)**

HR, hazard ratio; CI, confidence interval; ICD-10, International Classification of Diseases, tenth revision; NHL, non-Hodgkins lymphoma

[a] mortality rate / 10,000 person-years, [b] analyzed until the end of 2017, [c] HR for combined gastrointestinal cancers (cancers of the liver, pancreas and gastrointestinal tract) 1.21 (95% CI 0.94-1.56), [d] anal cancer not included, [e] analyzed only for females, [f] analyzed only for males

Table 3. Specific relative mortality risks in celiac patients compared to reference individuals in the peri- and post-diagnostic period.

Cause of death	Peri-diagnostic period (<2 years after diagnosis), n (deaths) = 708		Post-diagnostic period (≥2 years after diagnosis) [a], n (deaths) = 2,355	
	HR	95% CI	HR	95% CI
All causes	1.07	0.90–1.26	1.00	0.91–1.10
All malignancies	1.41	1.07–1.86*	1.02	0.86–1.20
Gastrointestinal tract malignancies	2.18	1.14–4.15*	1.07	0.72–1.59
Lymphoproliferative diseases	5.07	2.55–10.06**	1.71	1.10–2.66*
Digestive diseases	3.54	1.59–7.90*	1.75	1.01–3.05*

HR, hazard ratio; CI, confidence interval

[a] The results were not significantly different when the follow-up was analyzed in time periods < 1, 1-5, and over 5 years.

* $P < 0.05$, ** $P < 0.001$

Table 4. Studies on overall risk of mortality and mortality for lymphoproliferative diseases (non-Hodgkins lymphoma) in diagnosed coeliac disease patients.

Study, Year	Country	Age group	Number of CD patients	Years of diagnosis or enrollment	Person-years for CD patients	Overall mortality Risk estimate (95% CI)	Mortality for lymphoproliferative diseases Risk estimate (95% CI)
Cottone et al. 1999 (50)	Italy	Adults	216	1980–1997	ND	SMR 3.8 (2.0–7.0)	-
Corrao et al. 2001 (17)	Italy	Adults	1,072	1962–1994	6,444	SMR 2.0 (1.5–2.7)	SMR 69.3 (40.7–112.6) for NHL
Peters et al. 2003 (10)	Sweden	Mixed [a]	10,032	1964–1993	81,182	SMR 2.0 (1.8–2.1)	SMR 11.4 (7.8–16.0) for NHL
West et al. 2004 (13)	UK	Mixed [b]	4,732	1987–2002	18,923	HR 1.3 (1.1–1.5)	-
Viljamaa et al. 2006 (38)	Finland	Mixed [c]	781	1960–2000	10,956	SMR 1.3 (1.0–1.6)	SMR 4.1 (1.7–8.5)
Solaymani-Dodaran et al. 2007 (40)	UK	Adults	340	1961–1981	6,240	SMR 1.6 (1.3–1.8)	SMR 14.4 (7.4–25.0)
Ludvigsson et al. 2009 (12)	Sweden	Mixed [d]	29,096	1969–2008	ND	HR 1.4 (1.3–1.5)	-
Grainge et al. 2011 (41)	UK	Mixed [e]	1,092	1958–2006	10,152	SMR 1.4 (1.2–1.6)	SMR 7.1 (2.6–15.4) for NHL
Abdul Sultan et al. 2015 (19)	UK	Mixed [f]	10,825	1998–2012	60,226	HR 0.9 (0.8–1.0)	-
Holmes & Muirhead 2018 (11)	UK	Adults	2,174	1978–2014	23,955	SMR 1.6 (1.4–1.8)	SMR 6.3 (2.9–12.0)
Present study [g]	Finland	Adults	12,803	2005–2014	99,094	HR 1.0 (0.9–1.1)	HR 2.4 (1.7–3.4)

CD, celiac disease; NHL, non-Hodgkin lymphoma; ND, not defined; SMR, standardized mortality ratio; HR, hazard ratio
Proportion of patients diagnosed as children or adolescents: [a] 70%, [b] 12%, [c] ND, [d] 41%, [e] 10%, [f] 13%
[g] dermatitis herpetiformis patients included

Figure Legend

Figure 1. Mortality rates for lymphoproliferative diseases in different diagnostic age groups.
HR, hazard ratio; CI, confidence interval; * $P < 0.05$