ORIGINAL INVESTIGATION

Causes of Death in Patients With Celiac Disease in a Population-Based Swedish Cohort

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Background: Patients with celiac disease have an increased risk of death from gastrointestinal malignancies and lymphomas, but little is known about mortality from other causes and few studies have assessed long-term outcomes.

Methods: Nationwide data on 10 032 Swedish patients hospitalized from January 1, 1964, through December 31, 1993, with celiac disease and surviving at least 12 months were linked with the national mortality register. Mortality risks were computed as standardized mortality ratios (SMRs), comparing mortality rates of patients with celiac disease with rates in the general Swedish population.

Results: A total of 828 patients with celiac disease died during the follow-up period (1965-1994). For all causes of death combined, mortality risks were significantly elevated: 2.0-fold (95% confidence interval [CI], 1.8-2.1) among all patients with celiac disease and 1.4-fold (95% CI, 1.2-1.6) among patients with celiac disease with no other discharge diagnoses at initial hospitalization. The overall SMR did not differ by sex or calendar year of initial hospitalization, whereas mortality risk in patients hospitalized with celiac disease before the age of 2 years was significantly lower by 60% (95% CI, 0.2-0.8) compared with the same age group of the general population. Mortality risks were elevated for a wide array of diseases, including non-Hodgkin lymphoma (SMR, 11.4), cancer of the small intestine (SMR, 17.3), autoimmune diseases (including rheumatoid arthritis [SMR, 7.3] and diffuse diseases of connective tissue [SMR, 17.0]), allergic disorders (such as asthma [SMR, 2.8]), inflammatory bowel diseases (including ulcerative colitis and Crohn disease [SMR, 70.9]), diabetes mellitus (SMR, 3.0), disorders of immune deficiency (SMR, 20.9), tuberculosis (SMR, 5.9), pneumonia (SMR, 2.9), and nephritis (SMR, 5.4).

Conclusion: The elevated mortality risk for all causes of death combined reflected, for the most part, disorders characterized by immune dysfunction.

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CELIAC DISEASE is a disorder characterized by permanent intolerance to the protein gluten, which is contained in grains such as wheat, rye, or barley, and manifested by inflammation of the small intestine in genetically susceptible individuals. Typical symptoms include diarrhea and weight loss, but many patients, especially adults, have only mild or atypical symptoms. The widely accepted basis for the diagnosis of celiac disease is a biopsy to confirm the jejunal villous atrophy.[1,2] The prevalence of celiac disease ranges from 0.1 celiac patient per 1000 live births in Denmark, Finland, Germany, Spain, New Zealand, and the United States to approximately 3 per 1000 live births in Ireland.[3-5] In Sweden, a high prevalence of childhood-onset celiac disease has been noted, but it is unclear to what extent this pattern reflects changes in infant exposure to gliadin (eg, through early introduction of cereal drinks).[3,6] The reported prevalence of the disease in the United States seems to be somewhat low in light of the genetic similarities and European ancestry of many white Americans. Since serologic screening tests, such as antigliadin and antiendomysium antibody assays, have become more widely available in the last decade, it now seems that celiac disease is widely underdiagnosed,[7-10] including in the United States.[11-16] Recent population-based screening studies in several European countries have shown that prevalence of celiac disease is much higher (eg, 2 to 10 patients per 1000 individuals) than previously reported,[10,17-20] making celiac disease one of the most common genetically based human diseases.[21,22]

Celiac disease is associated with malignant neoplasms of the gastrointestinal tract, non-Hodgkin lymphoma,[23-31] and a variety of nonmalignant diseases such as

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autoimmune disorders, liver diseases, and osteoporosis.[25,32-37] There is growing evidence that the associated serious disease outcomes linked with celiac disease could be reduced by a strict adherence to a lifelong gluten-free diet, the only effective therapy.[23,33,38-40] Several generally small studies[25,29,40-42] also suggest an increased overall mortality in patients with celiac disease. The Swedish In-patient Registry provided a unique opportunity to investigate mortality risks in more than 10 000 patients with celiac disease, assess time trends throughout 30 years of follow-up, and examine long-term, cause-specific mortality outcomes, thus providing further information about the lifetime natural history of celiac disease.

METHODS

CELIAC DISEASE COHORT

A detailed description of the Swedish In-patient Registry has been published elsewhere.[43] Briefly, the Swedish National Board of Health and Welfare has collected individual-based data on hospital discharges on a countywide level since 1964, which has been expanded to nationwide data collection since 1987. Each record of the Swedish In-patient Registry includes an individual's personal identification number, date of birth, and sex; dates of hospital admission and discharge; the hospital department in which the patient was treated; and up to 8 discharge diagnoses. The diagnoses were coded according to the *International Classification of Diseases, Seventh Revision* (*ICD-7*) through 1968, the eighth revision (*ICD-8*) through 1986, and the ninth revision (*ICD-9*) thereafter. This study was approved by the Ethics Committee, Uppsala University (Uppsala, Sweden), and by the Swedish Data Inspection Board. We selected all records in the Swedish In-patient Registry with a discharge diagnosis of celiac disease (*ICD-7* code, 286.00; *ICD-8* codes, 269.00 and 269.98; and *ICD-9* code, 579.0). Between January 1, 1964, and December 31, 1993, the records selected reporting at least one hospitalization for celiac disease included a total of 11 455 unique personal national registration numbers.

We linked the personal national registration numbers provided on those computerized records to the nationwide population register and register of cause of death to assess migration and vital status. We excluded 390 records (3.4%) with incomplete or nonmatching identification numbers and 4 records with inconsistent dates. Of the remaining 11 061 patients with valid personal national registration numbers, we excluded 1029 patients (9.3%) who died, emigrated, or were lost to follow-up within 12 months of hospitalization with a discharge diagnosis of celiac disease. We also excluded the first year of follow-up from the analysis to minimize selection bias because the outcome (mortality) is related to the likelihood of being hospitalized. Thus, 10 032 patients with celiac disease were included in our analysis.

STATISTICAL ANALYSIS

Follow-up began 12 months after the date of discharge from the index hospitalization and continued until emigration, death, or the end of the observation period (December 31, 1993), whichever event occurred first. We calculated the expected number of deaths by multiplying the observed person-years of follow-up by the corresponding age-, sex-, and calendar year–specific mortality rates in each stratum for the entire Swedish population. Mortality risks were estimated by calculating standardized mortality ratios (SMRs), which are defined as the ratio of the number of observed to the expected number of deaths. We calculated the 95% confidence intervals (CIs) of the SMRs, assuming that the observed cases follow a Poisson distribution.[44]

Stratified analyses were conducted to assess mortality risks by sex, length of follow-up (1-4, 5-9, ≥10 years), calendar year of entry into the cohort (defined as hospitalization during 1964-1979 vs 1980-1993), age at initial hospitalization (0-1, 2-9, 10-19, 20-39, 40-59, 60-69, ≥70 years), age at death (0-4, 5-19, 20-39, 40-59, 60-69, ≥70 years), and whether patients had a single discharge diagnosis of celiac disease or celiac disease in conjunction with additional discharge diagnoses. The choice of the cut points used for age at initial hospitalization was based on developmental characteristics of the human immune system.[33,45-48] We evaluated whether there were any statistically significant differences within the age strata by applying the χ^2 test for homogeneity and whether there were any statistically significant changes over time in SMR by calculating the χ^2 test for trend.[44]

RESULTS

For the 10 032 patients hospitalized for celiac disease, there were 81 182 person-years of follow-up, for an average length of follow-up of 8.1 years (range, 1-30 years) (**Table 1**). More than half of the patients were younger than 2 years at initial hospitalization; the average age at initial hospitalization was 17.4 years. A total of 828 patients (8.3%) died, with few deaths before the age of 40 years, more than half after the age of 60 years, and an average age at death of 68.6 years.

Overall, mortality risk was 2-fold increased in patients with celiac disease compared with that in the general Swedish population (Table 1). Risks for all causes of death combined did not differ by sex and were similar during all calendar year periods evaluated (1964-1993) (Table 1). We observed a slight decrease in the overall mortality risk with an increasing number of years of follow-up (*P* for trend = .004) (Table 1). After excluding deaths from cardiovascular diseases, the SMRs for all other causes of death were 2.5 (95% CI, 2.1-2.8), 2.5 (95% CI, 2.1-2.9), and 2.0 (95% CI, 1.7-2.4) for follow-up intervals of 1 to 4 years, 5 to 9 years, and 10 or more years, respectively (*P* for trend = .12).

Patients who were initially hospitalized when younger than 2 years had a significantly lower mortality risk, whereas patients initially hospitalized at 2 years or older had an increased mortality risk compared with the same age groups of the general population (Table 1). Of the 11 patients dying among those initially hospitalized with celiac disease before the age of 2 years, 4 died of malignant neoplasms (which included no cases of non-Hodgkin lymphoma or carcinoma of the small intestine), 2 from endocrine, nutritional, and metabolic diseases, 1 from aplastic anemia, 1 from a disease of the nervous system and sense organs, 1 from a congenital or perinatal disorder, and 2 from external causes. Although 70% of the patients entered the cohort before the age of 20 years (most of them before the age of 2 years), only 30 deaths (3.6% of the total) occurred in this age group. Highest risks were observed in patients initially hospitalized between the ages of 10 and 40 years, but the absolute number of deaths (n = 47) was relatively small

Table 1. Characteristics and SMRs for All Causes of Death Among a Cohort of Patients With Celiac Disease From the Swedish In-patient Registry (1964-1993, Follow-up >1 y)

Characteristics	No. of Persons	Person-Years	No. of Deaths	SMR (95% CI)
All patients	10 032	81 182	828	2.0 (1.8-2.1)
Sex				
Male	4170	34 936	419	1.9 (1.8-2.1)
Female	5862	46 246	409	2.0 (1.8-2.2)
Length of follow-up, y				
1-4	10 032	26 713	335	2.2 (1.9-2.4)
5-9	7750	30 023	289	2.0 (1.8-2.2)
≥10	4443	24 447	204	1.7 (1.5-2.0)
Calendar year of initial hospitalization				
1964-1979	2576	38 546	384	2.1 (1.9-2.3)
1980-1993	7456	42 636	444	1.9 (1.7-2.1)
Age at initial hospitalization, y				
0-1	4953	41 328	11	0.4 (0.2-0.8)
2-9	1659	14 640	11	2.2 (1.1-3.9)
10-19	441	3218	8	5.3 (2.3-10.5)
20-39	697	7032	39	3.5 (2.5-4.7)
40-59	1086	8940	203	2.6 (2.3-3.0)
60-69	574	3647	243	2.2 (1.9-2.5)
≥70	622	2377	313	1.7 (1.5-1.9)
Age at death, y				
0-4			5	0.3 (0.1-0.6)
5-19			18	2.3 (1.4-3.6)
20-39			24	4.3 (2.4-7.0)
40-59			122	3.3 (2.5-4.1)
60-69			176	3.1 (2.5-3.7)
≥70			483	1.7 (1.6-1.9)
Other discharge diagnosis*				
No	6454	53 667	238	1.4 (1.2-1.6)
Yes/primary or secondary	3578	27 515	590	2.4 (2.2-2.6)
Yes/primary	1421	11 623	203	2.1 (1.8-2.4)
Yes/secondary	2157	15 892	387	2.5 (2.3-2.8)

Abbreviations: CI, confidence interval; SMRs, standardized mortality ratios.

*Yes/primary indicates that celiac disease was the first discharge diagnosis listed; yes/secondary, celiac disease was the second discharge diagnosis listed.

in this age group (Table 1). Although 67.1% of all deaths occurred in patients 60 years or older at initial hospitalization, this age group accounted for only 11.9% of all patients in the cohort. Similar trends were seen when risks were evaluated according to age at death as were observed for age at initial hospitalization (Table 1).

Approximately two thirds of patients (64.3%) had celiac disease listed as a single discharge diagnosis at initial hospitalization (Table 1). Patients whose initial hospitalization included discharge diagnoses for celiac disease and other medical conditions had a higher mortality risk (SMR, 2.4) than patients whose initial hospitalization included the single discharge diagnosis of celiac disease (SMR, 1.4). Although 590 (71.3%) of the deaths occurred in patients initially hospitalized with celiac disease and other discharge diagnoses, the differences between the SMRs of those with vs those without other discharge diagnoses must be interpreted in light of the notable age difference between the 2 groups. Those without other discharge diagnoses were on average 10.7 years old at initial hospitalization, whereas patients with celiac disease and other discharge diagnoses were on average 29.5 years old at initial hospitalization (data not shown).

Among the entire population of patients with celiac disease, cardiovascular diseases were the leading cause of death in both men and women, comprising 39.4% of all deaths, followed by malignant neoplasms as the second leading cause (19.4%) and then digestive diseases (12.1%) and respiratory diseases (9.8%) in both sexes (**Table 2**).

Infectious conditions comprised only 1.2% of deaths but were linked with high SMRs, including a 5.9-fold excess mortality from tuberculosis and 7.1-fold excess mortality from septicemia (Table 2). Although not included in the major *ICD* category designated as "infectious conditions," patients with celiac disease also experienced excess mortality risk from pneumonia and bronchopneumonia (SMR, 2.9).

Mortality from all malignant neoplasms combined was elevated 70% and was particularly high for cancer of the small intestine, non-Hodgkin lymphoma, and liver cancer. After excluding these 3 cancer sites, the mortality risks for all remaining malignant neoplasms were 30% increased (95% CI, 1.1-1.6). Mortality from colon cancer was significantly increased in women (SMR, 3.2) but not in men (SMR, 0.9) (a significant sex difference, $P=.03$).

The significantly increased SMRs for the combined category of endocrine, nutritional, metabolic, and immunologic disorders was primarily due to diabetes mellitus (comprising about half of the deaths), hypothyroidism, and disorders of immune deficiency, the latter 2 characterized by high mortality risks (Table 2). One patient died of cystic fibrosis.

Patients with celiac disease had a 6.4-fold excess risk of dying from diseases of the blood and blood-forming organs, but these outcomes (including 3 from aplastic anemia and 1 each from pernicious anemia, hereditary hemolytic anemia, other unspecified anemia, and agranulocytosis) were diverse and represented only 0.8% of deaths (Table 2). The overall increased SMR for the combined category of diseases of the nervous system and sense organs (Table 2) was also due to a variety of different diseases.

Mortality risk for cardiovascular diseases was 60% increased (Table 2); risks were similar for ischemic heart disease, other pulmonary heart disease, and cerebrovascular diseases.

The 7.9-fold excess mortality risk for all digestive system diseases combined included a high SMR associated with celiac disease, but deaths from celiac disease represented only 2.9% of the total deaths (Table 2). The SMRs for inflammatory bowel diseases, vascular insufficiency of the intestine, chronic liver diseases, and diseases of the pancreas were between 5- and 70-fold increased (Table 2). The 12 deaths from inflammatory bowel diseases included 6 from ulcerative colitis and 6 from Crohn disease. Among the 24 patients who died of chronic liver diseases (Table 2), 4 were ascribed to biliary cirrhosis, 15 to unspecified chronic liver diseases without mention of alcohol, and 5 to alcoholic liver cirrhosis. The mortality from liver cirrhosis was notably and significantly ($P=.004$) higher within years 2 to 4 following ini-

Table 2. Standardized Mortality Ratios (SMRs) for Specific Causes of Death Among a Cohort of Patients With Celiac Disease From the Swedish In-patient Registry (1964-1993, Follow-up >1 y)

		Patients With No Other Discharge Diagnosis			All Patients		
Cause of Death	*ICD-9* Code	Observed Deaths, No.	Expected Death, No.*	SMR (95% CI)	Observed Deaths, No.	Expected Deaths, No.*	SMR (95% CI)
All causes	000-999	238	169.0	1.4 (1.2-1.6)	828	419.3	2.0 (1.8-2.1)
Infections and parasitic conditions	000-139	4	1.6	2.5 (0.7-6.4)	10	3.4	2.9 (1.5-2.0)
Tuberculosis	010-018, 137	1	0.3	3.8 (0.1-21.0)	4	0.7	5.9 (1.6-15.1)
Septicemia	038	1	0.3	3.4 (0.0-19.1)	4	0.6	7.1 (1.9-18.2)
Malignant neoplasms	140-208	70	38.3	1.8 (1.4-2.3)	161	92.5	1.7 (1.5-2.0)
Small intestine	152	1	0.1	8.3 (0.1-46.4)	5	0.3	17.3 (5.6-40.3)
Large intestine, except rectum	153	6	3.0	2.0 (0.7-4.4)	16	7.5	2.1 (1.2-3.5)
Liver and intrahepatic bile ducts	155	1	1.0	1.0 (0.0-5.5)	10	2.5	4.0 (1.9-7.4)
Gallbladder and bile ducts	156	2	1.2	1.7 (0.2-6.0)	4	3.0	1.4 (0.4-3.5)
Pancreas	157	8	2.6	3.1 (1.3-6.1)	18	6.3	2.8 (1.7-4.5)
Non-Hodgkin lymphoma	200, 202	22	1.2	18.0 (11.3-27.2)	33	2.9	11.4 (7.8-16.0)
Endocrine, nutritional, and metabolic diseases, and immune disorders	240-279	4	3.1	1.3 (0.3-3.2)	35	7.8	4.5 (3.1-6.2)
Hypothyroidism (unspecified)	244	0	0.0		3	0.0	64.5 (13.0-188.6)
Diabetes mellitus	250	1	2.3	0.4 (0.0-2.4)	18	6.0	3.0 (1.8-4.7)
Disorders of immune deficiency	279	2	0.1	15.9 (1.8-57.5)	5	0.2	20.9 (6.8-48.9)
Diseases of blood and blood-forming organs	280-289	4	0.5	8.9 (2.4-22.7)	7	1.1	6.4 (2.6-13.2)
Aplastic anemia	284	2	0.2	11.2 (1.3-40.6)	3	0.4	7.5 (1.5-21.9)
Diseases of nervous system and sense organs	320-389	5	2.6	1.9 (0.6-4.5)	14	5.2	2.7 (1.5-4.5)
Diseases of circulatory system	390-459	72	74.9	1.0 (0.8-1.2)	326	205.5	1.6 (1.4-1.8)
Ischemic heart disease	410-414	39	44.2	0.9 (0.6-1.2)	183	119.6	1.5 (1.3-1.8)
Other nonpulmonary heart disease	420-429	11	7.5	1.5 (0.7-2.6)	43	21.1	2.0 (1.5-2.7)
Cerebrovascular disease	430-438	11	14.8	0.7 (0.4-1.3)	59	41.2	1.4 (1.1-1.9)
Respiratory diseases	460-519	18	10.3	1.8 (1.0-2.8)	81	28.5	2.8 (2.3-3.5)
Pneumonia or bronchopneumonia	480-486, 507	12	6.0	2.0 (1.0-3.5)	50	17.4	2.9 (2.1-3.8)
Asthma	493	1	0.9	1.1 (0.0-6.2)	6	2.1	2.8 (1.0-6.2)
Diseases of digestive system	520-579	39	4.9	7.9 (5.6-10.8)	100	12.7	7.9 (6.5-9.7)
Gastric and duodenal ulcers	531-534	2	0.9	2.2 (0.3-8.0)	8	2.5	3.2 (1.4-6.4)
Inflammatory bowel diseases	555, 556	5	0.1	68.5 (22.1-159.8)	12	0.2	70.9 (36.6-123.9)
Vascular insufficiency of intestine	557	2	0.3	6.9 (0.8-25.0)	4	0.8	5.0 (1.4-12.9)
Liver cirrhosis	571	4	1.4	2.9 (0.8-7.4)	24	3.1	7.8 (5.0-11.6)
Diseases of the pancreas	577	2	0.3	7.7 (0.9-27.7)	5	0.6	8.1 (2.6-18.8)
Celiac disease	579	16	0.0	1063.0 (607.2-1726.4)	24	0.0	705.9 (452.1-1050.3)
Urinary diseases	580-599	4	1.7	2.3 (0.6-5.9)	13	4.9	2.7 (1.4-4.6)
Nephritis	580-583	2	0.3	6.6 (0.7-23.8)	4	0.7	5.4 (1.4-13.8)
Diseases of skin and subcutaneous tissue	680-709	0	0.1		2	0.4	5.0 (0.6-18.2)
Diseases of musculoskeletal system and connective tissue	710-739	2	0.7	2.7 (0.3-9.8)	15	1.8	8.3 (4.7-13.7)
Rheumatoid arthritis	714	0	0.3		6	0.8	7.3 (2.7-15.9)
Diffuse diseases of connective tissue	710	1	0.2	6.2 (0.1-34.6)	6	0.4	17.0 (6.2-37.1)
External causes	800-999	14	12.0	1.2 (0.6-2.0)	44	23.8	1.8 (1.3-2.5)

Abbreviations: CI, confidence interval; *ICD-9, International Classification of Diseases, Ninth Revision.*

*Expected number of deaths is defined as the number of deaths that would be expected for the Swedish population if the Swedish population would have the same age and sex distribution as the celiac cohort for the period of follow-up.

tial hospitalization for celiac disease (SMR, 13.9) than after the fourth year of follow-up (SMR, 4.5). Furthermore, mortality risks associated with liver cirrhosis were close to 3-fold and significantly ($P=.004$) higher in women (SMR, 13.7) than in men (SMR, 4.2).

One of 2 deaths from diseases of the skin and subcutaneous tissue was due to dermatitis herpetiformis (SMR, 39.0; 95% CI, 0.5-217.1). Although dermatitis herpetiformis was the underlying cause of death in only 1 celiac patient, dermatitis herpetiformis was a discharge diagnosis in 221 (2.2%) of all patients with celiac disease. The overall SMR among the 221 patients with both dermatitis herpetiformis and celiac disease was 1.4 (95% CI, 0.5-3.1), lower than the 2.0-fold excess among all patients with celiac disease.

The 8.3-fold increased mortality risks from diseases of the musculoskeletal system and connective tissue were mainly from deaths due to autoimmune diseases (12 of 15 total), including 6 from rheumatoid arthritis, 2 from diffuse diseases of connective tissue, 2 from polymyositis, and 1 death each from systemic sclerosis and Sjögren syndrome.

Fifty-four patients in the celiac disease cohort (0.5%) also had discharge diagnoses of Down syndrome. The only death of a patient with both celiac disease and Down syndrome occurred less than 12 months after the hospitalization for celiac disease.

Most cause-specific SMRs in patients with celiac disease initially hospitalized with no other discharge diagnosis were similar to the cause-specific SMRs observed in all patients with celiac disease (Table 2). However, the excess mortality risks for cardiovascular diseases were not observed in patients initially hospitalized for celiac disease alone but were limited to celiac cases initially hospitalized with one or more additional discharge diagnoses (SMR, 1.9; 95% CI, 1.7-2.2). Furthermore, mortality rates from hypothyroidism, diabetes mellitus, asthma, and rheumatoid arthritis were not increased in patients with celiac disease alone but were significantly increased in the entire population of patients with celiac disease (Table 2).

COMMENT

This population-based Swedish cohort study of mortality risks in patients with celiac disease is one of the largest and longest in length of follow-up, providing an opportunity to investigate long-term, subgroup, and cause-specific mortality outcomes. Overall, mortality from all causes of death combined was 2-fold increased. Risks were similar by sex and calendar year period of initial hospitalization. Mortality risks for patients with celiac disease with no other discharge diagnosis at initial hospitalization were lower compared with risks for the entire population of patients with celiac disease, but risks for the former were still significantly increased. Whereas mortality risk was decreased overall in children initially hospitalized with celiac disease before the age of 2 years, risks were elevated in patients initially hospitalized with celiac disease at 2 years or older. Higher risks were observed for a wide array of conditions characterized by disturbances of immune function.

Only 5 prior studies,[25,29,40-42] to our knowledge, evaluated mortality risks associated with celiac disease, with the total number of outcomes ranging from 11 to 115 deaths compared with 828 in the current investigation. Similar to the present study, overall SMRs were approximately 2.0 in the next 2 largest studies (conducted in United Kingdom[41] and Italy[40]), whereas SMRs of 3.4, 3.8, and 1.0 were found in the substantially smaller investigations conducted in Denmark,[29] Italy,[42] and Finland,[25] respectively.

Logan et al[41] and Corrao et al[40] described a decline in mortality risk with increasing time after diagnosis. Although we do not have precise information on the age at diagnosis of celiac disease among cohort patients, we did not see such a decline after excluding deaths from diseases of the circulatory system. Because the excess mortality from circulatory diseases was limited to patients initially hospitalized with discharge diagnoses other than celiac disease, the statistical association of celiac disease with circulatory diseases seemed unlikely to be causal.

Our study found increased mortality from the combined group of all malignant neoplasms, similar to results from studies in the United Kingdom[41,49] and Italy.[40] The high SMRs for cancer of the small intestine and non-Hodgkin lymphoma in the present investigation are consistent with the increased incidence for these neoplasms in previous studies[24,26-30] and an analysis of cancer incidence of our cohort.[31] Non-Hodgkin lymphoma has been linked with disorders that involve dysfunction of the immune system, including acquired immunodeficiency syndrome, organ transplantation, or certain autoimmune disorders.[50-52] Swedish patients hospitalized with celiac disease experienced increased mortality risks from disorders characterized by immune dysfunction, including rheumatoid arthritis, diffuse diseases of connective tissue, inflammatory bowel diseases, diabetes mellitus, and asthma, and by infections involving disturbed immunity, such as tuberculosis and pneumonia.

Similar to our study, earlier investigations[25,33-36,53-55] have also demonstrated an increased prevalence of certain autoimmune disorders in patients with celiac disease. Although the pathophysiologic mechanisms that characterize celiac disease are not fully understood, recent studies point to autoimmune-related aspects, since approximately 95% of patients with celiac disease carry an almost identical HLA DQ2/heterodimer.[56] The HLA DQ2 haplotype (B8, DR3) has been linked with various autoimmune diseases.[25,57-59] It has been hypothesized that the immune-mediated disease mechanisms that may predispose to autoimmune diseases in patients with celiac disease may result from gluten-stimulated production of certain antibodies, such as tissue transglutaminase and fibroblast-derived extracellular matrix protein. These antibodies, found in the intestine and elsewhere,[9,33,60,61] also have been described in patients with dermatitis herpetiformis.[62,63] The mortality rate from inflammatory bowel diseases was somewhat higher than the mortality rates from other autoimmune disorders, possibly due to misdiagnosis of celiac disease (associated with an extremely high mortality rate) as inflammatory bowel disease.

The excess of liver cirrhosis observed in patients with celiac disease is partly explained by the increased occurrence of biliary cirrhosis.[64] Both biliary and small bowel epithelia may share susceptibility to an attack by autoimmune mechanisms.[65] The association of liver cirrhosis with chronic hepatitis in celiac disease may be mediated by the genetically determined association of HLA-B8[37,66] and characterized by aberrant T-cell function, antigen absorption from the gut, and immune complex formation.[25,67-69]

The increased mortality from tuberculosis and septicemia was consistent with earlier reports of severe infections in patients with celiac disease.[70-72] Splenic atrophy and/or hyposplenism occurs frequently in patients with celiac disease[37,73,74] and may predispose the patient to pneumonia and possibly other serious infections.

Mortality was notably increased from several diseases of the digestive system among patients with celiac disease, mostly due to deaths from autoimmune diseases that involve the gastrointestinal system. Nevertheless, it is possible that some of the increase of the gastrointestinal disorders may reflect increased surveillance and subsequent diagnoses and reporting of conditions that would otherwise go undetected.

Increased mortality in patients with celiac disease may also be related to reduced absorption of important nutrients, including vitamin A (linked with cancer of the upper gastrointestinal tract) and vitamin E (linked with neurologic disorders).[37,75] These complications may be worse among patients with a delayed diagnosis or those not following a strict gluten-free diet. Interestingly, we found a reduced mortality risk in patients initially hospitalized very early in life (before the age of 2 years) compared with the general Swedish population, although the youngest patients were only followed up until young adulthood. It is possible that some of the decreased mortality in young patients could reflect increased medical surveillance and earlier detection among children of high socioeconomic status; it was not possible to control for high socioeconomic status due to the limited variables related to socioeconomic status in the Swedish In-patient Registry database. If real, the decrease in mortality risk among the youngest patients may indicate different effects of gluten during different developmental stages of the immune system.[33,45-48] It will be important to continue to follow up the youngest patients in the Swedish In-patient Registry for many years to obtain a comprehensive picture of mortality throughout the lifespan for patients with celiac disease. The reduced mortality risk we observed to early adulthood for patients initially hospitalized at an early age may indicate that early diagnosis could potentially result in a reduced mortality in patients with celiac disease.

Strengths of our study include its population-based study design, the large cohort size, the lengthy period of follow-up, and the nearly complete ascertainment of mortality for various causes. Nevertheless, several limitations should be considered, including lack of information about potential confounders (such as smoking, alcohol intake, dietary information, compliance with a gluten-free diet, and socioeconomic status), histologic confirmation of diagnosis, and details of diagnostic examinations or specific treatments. However, the absence of excess mortality from lung cancer, other smoking-related malignancies, bronchitis, or emphysema suggests that prevalence of smoking was not higher in patients with celiac disease than the general population. In contrast, an increased mortality was found for liver cirrhosis in both sexes (with a diagnosis of alcoholism listed in only 5 of 24 deaths from liver cirrhosis) and for duodenal and gastric ulcers in men and external causes in both men and women.[76,77] It is therefore unclear whether some of the excess mortality could be due to alcoholism. Despite the absence of histologically confirmed jejunal villous atrophy and clinical information about a response to a gluten-free diet, it is unlikely that a substantial proportion of patients in the cohort lacked histologic confirmation, since biopsies were routinely performed on patients suspected of having celiac disease during the study period.[6,78,79] Limiting the cohort to hospital inpatients probably resulted in a disproportionate number of patients with celiac disease with more advanced disease and comorbidity. Although mortality in patients with celiac disease with other discharge diagnoses at initial hospitalization was higher than for those without other discharge diagnoses, our data suggest that this does not explain all of the excess mortality, since mortality remained significantly increased after excluding cases with other discharge diagnoses. A limitation of this and other mortality studies is the possible lack of specificity of diagnoses from the death certificates.

In summary, this large-scale, population-based cohort of hospitalized patients with celiac disease showed a 2-fold excess mortality from all causes combined, with little evidence that mortality risks changed over time, with increasing length of follow-up, or by sex. When the population was restricted to those with celiac disease but no other discharge diagnosis, overall mortality was lower but still significantly increased, and the findings were similar except for circulatory diseases, which were no longer elevated. Among this subgroup and the entire population of hospitalized patients with celiac disease, high mortality risks were observed for a variety of relatively uncommon specific disorders most consistently characterized by immune dysfunction. The Swedish patients with celiac disease experienced excess mortality from diseases of immunodeficiency, tuberculosis, pneumonia, autoimmune diseases, allergic disorders, and non-Hodgkin lymphoma. Risk of death was decreased for patients initially hospitalized with celiac disease early in life. This observation together with recognized beneficial effects of gluten-free diet[23,33,38-40] suggests that an early diagnosis and treatment of celiac disease may reduce mortality risk in these patients.

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