Small-Intestinal Histopathology and Mortality Risk in Celiac Disease

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Context Studies of mortality in celiac disease have not taken small-intestinal pathology into account.

Objective To examine mortality in celiac disease according to small-intestinal histopathology.

Design, Setting, and Patients Retrospective cohort study. We collected data from duodenal/jejunal biopsies taken between July 1969 and February 2008 on celiac disease (Marsh stage 3: villous atrophy; n=29 096 individuals) and inflammation (Marsh stage 1-2; n=13 306) from all 28 pathology departments in Sweden. A third cohort consisted of individuals with latent celiac disease from 8 university hospitals (n=3719). Latent celiac disease was defined as positive celiac disease serology in individuals with normal mucosa (Marsh stage 0). Through linkage with the Swedish Total Population Register, we estimated the risk of death through August 31, 2008, compared with age- and sex-matched controls from the general population.

Main Outcome Measure All-cause mortality.

Results There were 3049 deaths among patients with celiac disease, 2967 with inflammation, and 183 with latent celiac disease. We found an increased hazard ratio (HR) for death in celiac disease (HR, 1.39; 95% confidence interval [CI], 1.33-1.45; median follow-up, 8.8 years), inflammation (HR, 1.72; 95% CI, 1.64-1.79; median follow-up, 7.2 years), and latent celiac disease (HR, 1.35; 95% CI, 1.14-1.58; median follow-up, 6.7 years). The absolute mortality rate was 10.4 (95% CI, 10.0-10.8) per 1000 person-years in celiac disease, 25.9 (95% CI, 25.0-26.8) in inflammation, and 6.7 (95% CI, 5.7-7.6) in latent celiac disease. Excess mortality was 2.9 per 1000 person-years in celiac disease, 10.8 in inflammation, and 1.7 in latent celiac disease. This risk increase was also seen in children. Excluding the first year of follow-up, HRs decreased somewhat.

Conclusion Risk of death among patients with celiac disease, inflammation, or latent celiac disease is modestly increased.

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CELIAC DISEASE IS AN IMMUNE-mediated disorder that is triggered by gluten exposure in genetically sensitive individuals, occurring in about 1% of the Western population.

With few exceptions,[1] research has shown an increased risk of death in celiac disease[2-9] and in individuals with positive antiendomysial antibodies (EMA)[10] or either EMA or antigliadin.[11] However, several studies were not population-based[6,8] or were limited by their focus on inpatients,[5] less than 1000 individuals with celiac disease,[1,2,8-10] or lack of inclusion of children.[1,4,6]

The introduction of celiac disease serological markers has allowed screening of individuals with less marked symptoms; it is therefore possible that earlier studies (based on data until 2000[1,2,4-6,8,10,11]) overestimate the risk of death in celiac disease.

While villous atrophy is usually required for the diagnosis of celiac disease, less is known about the long-term consequences of nonspecific small-intestinal inflammation without villous atrophy. Research on other inflammatory disorders suggests that inflammation may be associated with increased mortality,[12-14] but this has not been investigated for nonspecific inflammation in the small intestine.

Some individuals have positive antibodies but normal small-intestinal mucosa, often referred to as having "latent" celiac disease.[15] Although villous atrophy in small-intestinal biopsy has been the gold standard for a celiac disease diagnosis,[15,16] it has been argued that small-intestinal biopsy can, under certain circumstances, be replaced by celiac disease serology.[17] Positive celiac disease serology has been linked to increased mortality[11]; however, the predictive value and long-term consequences of celiac disease serology in individuals with normal mucosa are unknown.

We used nationwide histopathology data to examine the overall risk of death in individuals with celiac disease and inflammation. Through regional data linkage, we were also able to examine mortality in latent celiac disease.

See also p 1225 and Patient Page.

METHODS

This retrospective cohort study estimated mortality in celiac disease according to small-intestinal histopathology. Nationwide histopathology data were matched with mortality data from government agencies in Sweden.

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Table 1. Characteristics of Study Participants

Characteristics	Celiac Disease (n = 29 096)	Inflammation (n = 13 306)	Latent Celiac Disease (n = 3719)[a]
Age at study entry, median (range), y	30 (0-95)	49 (0-99)	36 (0-91)
0-19	11 802 (40.6)	1226 (9.2)	941 (25.3)
20-39	5312 (8.3)	3456 (26.6)	1150 (30.9)
40-59	6477 (22.3)	4149 (31.2)	1064 (28.6)
≥60	5505 (18.9)	4385 (33.0)	564 (15.2)
Follow-up, median (range), y[b]	8.8 (0-39.1)	7.2 (0-33.3)	6.7 (0-18.4)
Follow-up, mean (SD), y[b]	10.1 (6.4)	8.6 (6.6)	7.4 (4.3)
Male, No. (%)	11 091 (38.1)	5809 (43.7)	1409 (37.9)
Calendar period			
≤1989	4105 (14.1)	1961 (14.7)	0
1990-1999	12 059 (41.4)	5164 (38.8)	1387 (27.3)
≥2000	12 932 (44.4)	6181 (46.4)	2332 (62.7)
Entry year, median (range)	1998 (1969-2008)	1999 (1970-2008)	2001 (1990-2007)

[a] Positive celiac disease serology 180 days before biopsy and until 30 days after biopsy. Immunoglobulin A endomysium: n=227; IgA tissue transglutaminase: n=159; IgA gliadins: n=3102; IgG endomysium: n=1; IgG tissue transglutaminase: n=4; IgG gliadins: n=491.
[b] Follow-up until death or August 31, 2008. In controls, follow-up also ended at time of any small-intestinal biopsy.

This study was approved by the Research Ethics Committee of Karolinska Institutet, Stockholm. Since none of the participants was contacted and individual information was anonymized prior to the analyses, informed consent was not required.

Collection of Biopsy Data

Between October 27, 2006, and February 12, 2008, we collected data from biopsies performed between July 1969 and February 2008 through computerized searches of all 28 regional pathology departments in Sweden, archived in 2 different computer systems. Small-intestinal biopsy before celiac disease diagnosis is standard practice in Sweden.[18] Searches were carried out by local technicians for (1) arrival date of the biopsies, (2) personal identification number (PIN),[19] (3) morphology according to Swedish SnoMed classification codes, and (4) topography (duodenum or jejunum). Since we used computer searches, we were unable to identify individuals with biopsy reports prior to computerization, and most patients therefore had provided a biopsy after 1990 (TABLE 1).

Morphology was graded using the Marsh classification[20] into villous atrophy (equal to celiac disease; Marsh stage 3), inflammation (Marsh stage 1-2), and normal mucosa (Marsh stage 0). The celiac disease diagnosis was based on histopathology (celiac disease = villous atrophy), and a positive celiac disease serology result was not required for this diagnosis. Where there were data on subtype of villous atrophy, participants were subdivided into partial (Marsh stage 3a) and subtotal/total (Marsh stage 3b + c) villous atrophy. A diagnosis of inflammation required a SnoMed code for inflammation in the duodenum or jejunum (Marsh stage 1-2) but never a biopsy with villous atrophy. In the most common histopathology classification used in Sweden during the study period (KVAST), such inflammation is equivalent to intraepithelial lymphocytosis.

After the exclusion of duplicates and biopsies with data irregularities (eg, biopsy date before birth or after death of the individual), 351 403 biopsy reports remained in 287 586 unique individuals (celiac disease: 29 148; inflammation: 13 446; and normal biopsy: 244 992). Details of data collection have been published.[18,21]

To identify individuals with latent celiac disease, serology was obtained for individuals having biopsies within the catchment areas of the biochemistry laboratories of 8 university hospitals (celiac disease: n=11 612; inflammation: n=5302; normal mucosa: n=121 952). Hence, data on celiac disease serology and latent celiac disease are regional. For each serology sample, we obtained data on date of test, type of test (antigliadin, EMA, or tissue transglutaminase [tTG]), antibody levels, IgA/IgG, and age-specific reference values at the time of testing. In this study, we defined latent celiac disease as having normal mucosa with positive celiac disease serology up to 180 days before biopsy and until 30 days after biopsy. A total of 3736 individuals fulfilled these criteria.

Records of all celiac disease, inflammation, or latent celiac disease cases were then sent to Statistics Sweden for matching with controls. Statistics Sweden removed those with incorrect PINs. We excluded individuals in whom the biopsy could potentially originate from the ileum(n=174), those with no matched control (n=27), and those without a serial number from Statistics Sweden, who could not be matched with mortality data (n=8). Hence, our study was based on 29 096 individuals with celiac disease, 13 306 with inflammation, and 3719 with latent celiac disease.

Controls

For each individual with celiac disease, inflammation, or latent celiac disease, Statistics Sweden identified up to 5 controls matched on age, sex, county, and calendar period through the Total Population Register,[22] which includes information on PIN, area of residence, sex, age, and civil status of all Swedish residents. Controls were sampled from all Swedish residents in whom the regional pathology registers did not indicate prior duodenal/jejunal biopsy. Statistics Sweden identified 229 800 controls. We then excluded 247 (0.1%) because of data irregularities and 921 who could not be matched, leaving 228 632 .

Mortality Data

We used mortality data from the Total Population Register to estimate overall mortality in individuals undergoing small-intestinal biopsy. Data on cause-specific mortality were obtained from the Swedish Cause of Death Registry. In 1995, the National Board of Health and Welfare received death certificates on 99.7% of all deaths. In a post hoc analysis, we estimated relative risks of deaths

from malignancy, cardiovascular disease, and respiratory disease because an earlier Swedish study[5] found them to be the most common causes of death in patients with celiac disease; we also included "other disease."

Education Level Data

From Statistics Sweden, we received data on education from the Education Register. We divided education into 4 groups: 9 years or less of primary and secondary school, 2 years of high school (usually programs for manual, clerical, or assistance work), 3 years of high school (theoretical programs), and college or university studies. We adjusted our data for education because earlier research indicates an inverse relationship between education and seeking medical care (and ascertainment of celiac disease)[23] and overall mortality.[24]

Statistical Analyses

We used Cox regression conditioned on age at first biopsy (and corresponding date in controls), sex, county, and calendar period to estimate risk of death. The proportional hazards assumptions were investigated by introducing pseudo–time-dependent covariates to estimate the hazard ratio (HR) as a function of time since biopsy. Homogeneity of HRs (ie, lack of effect modification) with respect to the matching variables and other potential confounders were investigated by introducing appropriate interaction terms in the model, and their statistical significance was tested by likelihood ratio tests.

Follow-up began on the date of first positive biopsy result (or normal mucosa in an individual in whom celiac disease serology was positive at that time) and corresponding date in controls. For overall death, follow-up ended on August 31, 2008, or earlier if the patient died. For subanalyses of cause-specific death, follow-up ended on December 31, 2005, because of the time lag between recording the cause of death and these data becoming available in the Swedish Cause of Death Registry. Patients who died before the end of the study or were lost to follow-up were censored in the statistical analyses. In controls, follow-up could also end if the individual had a biopsy result indicating celiac disease, inflammation, or latent celiac disease after matching.

In preplanned subanalyses, we stratified by phenotype according to biopsy characteristics (partial villous atrophy vs subtotal/total villous atrophy), sex, age (0-19, 20-39, 40-59, and ≥60 years at first biopsy), and calendar period of first biopsy (≤1989, 1990-1999, ≥2000). Incidence rates were calculated as number of events divided by number of person-years at risk and 95% confidence intervals (CIs) were estimated based on the normal approximation of the Poisson distribution or by exact intervals when the number of events was less than 25.

Attributable risk percentages were estimated as (1 – 1/HR) and attributable risk as attributable risk percentage × mortality rate among exposed. Excess deaths among exposed were estimated as attributable risk percentage × observed deaths among exposed, and expected deaths among exposed (assuming the mortality rate of controls) as observed deaths among exposed – excess deaths among exposed.

We also estimated the risk of overall death in a subset of 3392 individuals with villous atrophy and positive celiac disease serology. We did not estimate the risk of death in individuals with inflammation and positive celiac disease serology because of lack of cases. Serologic testing has been used routinely in celiac disease since the 1990s. Antigliadin antibody tests were common in the 1990s.[25] In the late 1990s, Swedish biochemistry laboratories gradually shifted to EMA. In the last 5 to 6 years, celiac disease serology usually has included both EMA and tTG.[26,27] The most person-years in individuals with latent celiac disease belonged to individuals positive for antigliadin. In a subanalysis, we assessed if risk of death was different in EMA and tTG IgA-positive individuals vs those with antigliadin antibodies or IgG EMA/tTG. All analyses were adjusted for education level.

Statistical significance was defined as 95% CIs for risk estimates not including 1.0. We used SPSS, version 16.0 (SPSS Inc, Chicago, Illinois), and SAS, version 9.1 (SAS Institute Inc, Cary, North Carolina), to perform the analyses.

A post hoc power analysis using a .05 level of significance and 80% power showed detectable relative risks with respect to overall mortality of 1.06, 1.06, and 1.27 for celiac disease, inflammation, and latent celiac disease, respectively.

RESULTS

Overall Mortality According to Histopathology

There were 3049 deaths among patients with celiac disease, 2967 deaths in inflammation, and 183 deaths in latent celiac disease. Mortality was increased in all 3 cohorts, with the highest HRs (adjusted for education) in patients with inflammation (HR, 1.72; 95% CI, 1.64-1.79), while HRs were similar in celiac disease (HR, 1.39; 95% CI, 1.33-1.45) and latent celiac disease (HR, 1.35; 95% CI, 1.14-1.58) (TABLE 2). The absolute mortality rate was 25.9 per 1000 person-years in inflammation (95% CI, 25.0-26.8), 10.4 in celiac disease (95% CI, 10.0-10.8), and 6.7 in latent celiac disease (95% CI, 5.7-7.6), and excess mortality was 10.8 per 1000 person-years in inflammation, 2.9 in celiac disease, and 1.7 in latent celiac disease. The higher absolute mortality among patients with inflammation is partly explained by their older age at study entry. Results were similar when not adjusted for education.

The HRs for mortality were highest in the first year of follow-up (Table 2), with celiac disease associated with a 2.80-fold increased risk of death, inflammation with a 4.66-fold increase, and latent celiac disease with a 1.81-fold increase. After the first year of follow-up, HRs decreased and were 1.26 for celiac disease, 1.41 for inflammation, and 1.27 for latent celiac disease. The absolute mortality rate when the first year of follow-up was excluded was 9.6 per 1000 person-years in celiac disease (95% CI, 9.2-10.0)(TABLE 3). Patients with inflammation had a higher mortality rate (22.0/1000 person-years; 95% CI, 21.1-22.9). The lowest absolute mortality rate was in latent celiac disease (6.6/1000 person-years; 95% CI, 5.6-7.6). After 5 years, the HR for death was 1.27 (95% CI, 1.20-

1.35) in celiac disease and 1.30 (95% CI, 1.22-1.38) in inflammation while the risk in latent celiac disease failed to attain statistical significance (HR, 1.11; 95% CI, 0.85-1.45).

Since HRs in the first year of follow-up were so different from that of later follow-up, we excluded the first year of follow-up from all subanalyses. Celiac disease is a lifelong disorder, and relative risks excluding the first year better estimate the long-term mortality risk.

Overall Mortality Subgroup Analyses

We examined the risk of mortality in individuals who underwent biopsy in childhood. There were few deaths (celiac disease: 7 deaths in first year after biopsy and 47 thereafter; inflammation: 1 and 5, respectively; latent celiac disease: 0 and 6, respectively). Despite this, there was an increased risk of death independent of histopathology (Table 3). The high relative mortality in latent celiac disease (HR, 8.87) after the first year of follow-up was based on only 6 deaths (expected count = 0.7). We retrieved data on cause of death in 4 of these cases (cystic fibrosis, pneumonia, congenital hydrocephalus, and unspecified malformation of the brain). We specifically examined mortality in childhood celiac disease according to follow-up and found similar HRs in the first year of follow-up (HR, 2.06; 95% CI, 0.83-5.14), between 1 and 5 years of follow-up (HR, 1.57; 95% CI, 0.86-2.86), and after more than 5 years of follow-up (HR, 1.90; 95% CI, 1.25-2.89). Because of few deaths, we did not examine mortality in inflammation and latent celiac disease in individuals who had biopsies in childhood according to follow-up.

Hazard ratios decreased with age at diagnosis, from 1.78 in celiac disease diagnoses before age 20 years to 1.18 in diagnoses at age 60 years or older. For inflammation, HRs decreased from 2.53 before age 20 years to 1.34 at age 60 years or older; for latent celiac disease, HRs decreased from 8.87 to 1.10 in those aged 20 to 39 years, to 1.25 in those aged 40 to 59 years, and to 1.21 in those aged 60 years or older (Table 3). Hazard ratios did not differ by sex or calendar period (Table 3).

The overall HR for mortality was higher in partial villous atrophy (HR, 1.33; 95% CI, 1.15-1.54) than in subtotal/total villous atrophy (HR, 1.13; 95% CI, 1.01-1.26; $P = .006$). The HR for mortality in patients with nonspecified villous atrophy was 1.28 (95% CI, 1.21-1.35).

Because of the recent introduction of celiac disease serology data, we compared individuals with villous atrophy with and without available celiac disease serology data. In 3392 individuals with villous atrophy and positive celiac disease serology data, mortality did not differ from that of individuals with villous atrophy without available celiac disease serology data ($P = .44$).

The HR for death in individuals with latent celiac disease and positive IgA EMA or IgA tTG results was not increased (HR, 0.49; 95% CI, 0.15-1.59). The corresponding HR for individuals with normal mucosa and positive IgA gliadin or IgG gliadin/EMA/tTG positivity was 1.35 (1.12-1.63). The difference in HRs between individuals with IgA EMA/tTG vs other positive antibodies was not statistically significant ($P = .28$).

Cause-Specific Mortality

Cardiovascular disease was the most common cause of death in celiac disease, followed by malignancy (TABLE 4). A similar pattern was seen in inflamma-

Table 2. Overall Mortality According to Follow-up Period[a]

Subgroup	Deaths, No. Observed	Deaths, No. Expected	Hazard Ratio (95% CI)	*P* Value	AMR per 1000 Person-Years (95% CI)	AR per 1000 Person-Years[b]	AR, % of AMR
Overall							
Controls	23 633		1 [Reference]				
Celiac disease	3049	2194	1.39 (1.33-1.45)	<.001	10.4 (10.0-10.8)	2.9	28.1
Inflammation	2967	1725	1.72 (1.64-1.79)	<.001	25.9 (25.0-26.8)	10.8	41.9
Latent celiac disease	183	136	1.35 (1.14-1.58)	<.001	6.7 (5.7-7.6)	1.7	25.9
Year <1							
Controls	1864		1 [Reference]				
Celiac disease	507	181	2.80 (2.51-3.11)	<.001	17.6 (16.1-19.2)	11.3	64.3
Inflammation	728	156	4.66 (4.23-5.14)	<.001	57.0 (52.8-61.1)	44.8	78.5
Latent celiac disease	26	14	1.81 (1.18-2.76)	.006	7.0 (4.3-9.7)	3.1	44.8
Year 1-5							
Controls	7316		1 [Reference]				
Celiac disease	863	707	1.22 (1.13-1.32)	<.001	8.5 (7.9-9.1)	1.5	18.0
Inflammation	880	543	1.62 (1.50-1.75)	<.001	21.5 (20.0-22.9)	8.2	38.3
Latent celiac disease	87	65	1.33 (1.06-1.67)	.02	7.1 (5.6-8.6)	1.8	24.8
Year >5							
Controls	14 453		1 [Reference]				
Celiac disease	1679	1322	1.27 (1.20-1.35)	<.001	10.3 (9.8-10.8)	2.2	21.3
Inflammation	1359	1045	1.30 (1.22-1.38)	<.001	22.4 (21.2-23.6)	5.2	23.1
Latent celiac disease	70	63	1.11 (0.85-1.45)	.43	6.1 (4.7-7.5)	0.6	9.9

Abbreviations: AMR, absolute mortality rate; AR, attributable risk; CI, confidence interval.
[a] Data are adjusted for education.
[b] Attributable risk = excess risk. Attributable risk percentage is the attributable risk/absolute mortality rate.

tion. Individuals with celiac disease, inflammation, and latent celiac disease had increased HRs for death from cardiovascular disease, malignancy, and respiratory disease but also from "other causes." The association between latent celiac disease and cardiovascular death, however, did not reach statistical significance (HR, 1.27; 0.91-1.76) (Table 4).

Table 3. Overall Mortality According to Histopathology, First Year Excluded[a]

Subgroup	Deaths, No. Observed	Deaths, No. Expected	HR (95% CI)	*P* Value	AMR per 1000 Person-Years (95% CI)	AR per 1000 Person-Years[b]	AR, % of AMR
Overall							
Controls	21 769		1 [Reference]				
Celiac disease	2542	2017	1.26 (1.20-1.32)	<.001	9.6 (9.2-10.0)	2.0	20.6
Inflammation	2239	1588	1.41 (1.34-1.48)	<.001	22.0 (21.1-22.9)	6.4	29.1
Latent celiac disease	157	124	1.27 (1.07-1.52)	.007	6.6 (5.6-7.6)	1.4	21.3
Sex							
Male							
Controls	11 352		1 [Reference]				
Celiac disease	1289	1007	1.28 (1.20-1.36)	<.001	13.0 (12.3-13.7)	2.8	21.9
Inflammation	1178	866	1.36 (1.27-1.46)	<.001	25.9 (24.5-27.4)	6.9	26.5
Latent celiac disease	71	51	1.39 (1.07-1.81)	.01	7.6 (5.9-9.4)	2.1	28.1
Female							
Controls	10 417		1 [Reference]				
Celiac disease	1253	1010	1.24 (1.16-1.32)	<.001	7.6 (7.2-8.0)	1.5	19.4
Inflammation	1061	726	1.46 (1.36-1.57)	<.001	18.8 (17.7-20.0)	5.9	31.5
Latent celiac disease	86	72	1.19 (0.94-1.51)	.15	6.0 (4.7-7.2)	1.0	16.0
Age at first biopsy, y							
<20							
Controls	152		1 [Reference]				
Celiac disease	47	26	1.78 (1.26-2.50)	.001	0.4 (0.3-0.5)	0.2	43.8
Inflammation	6	2.4	2.53 (1.01-6.36)	.05	0.6 (0.2-1.3)	0.4	60.5
Latent celiac disease	6	0.7	8.87 (3.09-25.5)	<.001	0.8 (0.3-1.8)	0.7	88.7
20-39							
Controls	488		1 [Reference]				
Celiac disease	107	55	1.96 (1.56-2.47)	<.001	2.2 (1.8-2.6)	1.1	49.0
Inflammation	70	40	1.75 (1.32-2.32)	<.001	2.3 (1.8-2.8)	1.0	42.9
Latent celiac disease	6	5.4	1.10 (0.46-2.61)	.83	0.8 (0.3-1.8)	0.1	9.1
40-59							
Controls	3595		1 [Reference]				
Celiac disease	546	390	1.40 (1.27-1.55)	<.001	8.9 (8.2-9.7)	2.6	28.6
Inflammation	421	255	1.65 (1.47-1.85)	<.001	11.8 (10.6-12.9)	4.6	39.4
Latent celiac disease	34	27	1.25 (0.86-1.81)	.25	5.4 (3.6-7.2)	1.1	20.0
≥60							
Controls	17 534		1 [Reference]				
Celiac disease	1842	1561	1.18 (1.12-1.25)	<.001	53.6 (51.2-56.1)	8.2	15.3
Inflammation	1742	1300	1.34 (1.26-1.41)	<.001	69.4 (66.1-72.6)	17.6	25.4
Latent celiac disease	111	92	1.21 (0.98-1.50)	.07	39.6 (32.3-47.0)	6.9	17.4
Year of first biopsy							
≤1989							
Controls	6816		1 [Reference]				
Celiac disease	755	609	1.24 (1.13-1.36)	<.001	9.7 (9.0-10.4)	1.9	19.4
Inflammation	742	523	1.42 (1.30-1.55)	<.001	23.9 (22.2-25.6)	7.1	29.6
Latent celiac disease	NA	NA					
1990-1999							
Controls	11 590		1 [Reference]				
Celiac disease	1370	1087	1.26 (1.19-1.34)	<.001	10.0 (9.5-10.6)	2.1	20.6
Inflammation	1153	860	1.34 (1.26-1.44)	<.001	22.6 (21.3-23.9)	5.7	25.4
Latent celiac disease	88	76	1.16 (0.92-1.47)	.21	5.8 (4.6-7.0)	0.8	13.8
≥2000							
Controls	3363		1 [Reference]				
Celiac disease	417	348	1.20 (1.08-1.34)	<.001	8.4 (7.6-9.2)	1.4	16.7
Inflammation	344	216	1.59 (1.40-1.79)	<.001	17.5 (15.6-19.3)	6.5	37.1
Latent celiac disease	69	50	1.39 (1.08-1.81)	.01	8.0 (6.1-9.9)	2.2	28.1

Abbreviations: AMR, absolute mortality rate; AR, attributable risk; CI, confidence interval; HR, hazard ratio; NA, not available.
[a] Data are adjusted for education.
[b] Attributable risk=excess risk. Attributable risk percentage is the attributable risk/absolute mortality rate.

The highest HRs were seen in the first year after biopsy, with an HR of 3.78 for death due to malignancy (95% CI, 3.14-4.55) and 1.86 for cardiovascular death (95% CI, 1.54-2.25). Death from respiratory disease (HR, 2.13; 95% CI, 1.34-3.40) and death from other causes (HR, 3.31; 95% CI, 2.60-4.19) were increased in the first year after celiac disease diagnosis. After 5 years of follow-up, cardiovascular mortality in celiac disease was only moderately increased (HR, 1.20; 95% CI, 1.09-1.33), as was death from malignancy (HR, 1.17; 95% CI, 1.03-1.33). Death from respiratory disease did not reach statistical significance (HR, 1.26; 95% CI, 0.98-1.62), while death from other causes was highest (HR, 1.58; 95% CI, 1.39-1.79).

COMMENT

In this population-based study, we examined risk of death in celiac disease according to small-intestinal histopathology. Excess mortality was observed independent of histopathology, but absolute excess mortality risk was small, especially in children.

This is the largest study of mortality in celiac disease, and the number of deaths (>3000) exceeds that of all earlier studies together.[1-11] Data on celiac disease and inflammation were collected from all pathology departments in Sweden. To our knowledge, this is the first population-based study of mortality in individuals with inflammation without villous atrophy and in latent celiac disease.[15]

Among the 29 000 patients with celiac disease, we found an HR for overall mortality of 1.39. This is less than in most earlier studies,[4-10] but previous research has often been based on inpatients[4,5] or few clinical units,[9] where selection bias favors inclusion of individuals with complicated disease. It is also likely that individuals with diagnoses before generally available autoantibody screening[1,2,4-6,8,10,11] were more often symptomatic and had high disease activity and, consequently, a higher mortality rate. In their study of 1072 celiac disease individuals from 11 centers, Corrao et al[6] found an increased risk of death in individuals with malabsorptive symptoms but not in individuals with minor symptoms (odds ratio, 1.1) or identified through screening (odds ratio, 1.2).

The mortality increase in celiac disease in our study is almost identical to that found among inpatients with celiac disease in Sweden without any other discharge diagnosis at hospital admission,[5] and in British individuals with celiac disease from the General Practice Research Database,[3] even though the study populations differ in time period, age, and representativeness.

We found a higher relative risk of mortality than did the study by Viljamaa et al,[2] which was based on individuals from 1 specialized unit who may have had better dietary adherence. Chart validation of 86 randomly selected patients with celiac disease in our cohort found low dietary adherence in 17%.[18]

We found a decreased HR for death over time in celiac disease, with the highest HRs in the first year after diagnosis. One explanation for the high initial estimates could be that some patients with severe preexisting morbidity undergo small-intestinal biopsy as part of a general investigation. This could also explain why we found high 1-year-risk estimates independent of histopathology. In patients with celiac disease, persisting inflammation, even after introduction of a gluten-free diet, may have contributed to the high HRs in the first year

Table 4. Cause-Specific Mortality According to Histopathology, First Year Included[a]

Subgroup	Deaths, No. Observed	Deaths, No. Expected	Hazard Ratio (95% CI)	*P* Value	AMR per 1000 Person-Years (95% CI)	AR per 1000 Person-Years[b]	AR, % of AMR
Cardiovascular							
Controls	9295		1 [Reference]				
Celiac disease	1007	846	1.19 (1.11-1.28)	<.001	4.0 (3.8-4.3)	0.6	16.0
Inflammation	979	725	1.35 (1.25-1.45)	<.001	10.1 (9.4-10.7)	2.6	25.9
Latent celiac disease	45	35	1.27 (0.91-1.76)	.16	2.1 (1.5-2.7)	0.4	21.3
Malignancy							
Controls	5141		1 [Reference]				
Celiac disease	773	499	1.55 (1.43-1.69)	<.001	3.1 (2.9-3.3)	1.1	35.5
Inflammation	876	378	2.32 (2.14-2.52)	<.001	9.0 (8.4-9.6)	5.1	56.9
Latent celiac disease	49	35	1.41 (1.03-1.93)	.03	2.3 (1.6-2.9)	0.7	29.1
Respiratory							
Controls	1338		1 [Reference]				
Celiac disease	165	121	1.36 (1.13-1.63)	.001	3.1 (0.6-0.8)	0.2	26.5
Inflammation	147	101	1.46 (1.20-1.78)	<.001	9.0 (1.3-1.8)	0.5	31.5
Latent celiac disease	11	3.9	2.83 (1.41-5.67)	.003	2.3 (0.2-0.8)	0.3	64.7
Other causes							
Controls	4329		1 [Reference]				
Celiac disease	672	407	1.65 (1.51-1.81)	<.001	2.7 (2.5-2.9)	1.1	39.4
Inflammation	628	312	2.01 (1.82-2.21)	<.001	6.5 (5.9-7.0)	3.2	50.2
Latent celiac disease	38	26	1.49 (1.04-2.13)	.03	1.8 (1.2-2.3)	0.6	32.9

Abbreviations: AMR, absolute mortality rate; AR, attributable risk; CI, confidence interval.
[a] Data are adjusted for education. Cause-specific mortality data are through December 31, 2005.
[b] Attributable risk=excess risk. Attributable risk percentage is the attributable risk/absolute mortality rate.

after biopsy, as normalization of the mucosa often takes up to a year. The decreased HR for death over time is consistent with earlier studies.[2-6]

This is also the largest study of mortality in children with celiac disease, with almost 12 000 individuals diagnosed in childhood. Two earlier studies reported an increased risk of mortality in celiac disease diagnosed in childhood.[5,7] Although we had a shorter follow-up than either earlier study, there were nevertheless more deaths (n=33) occurring after 5 years of follow-up. Unlike Solaymani-Dodaran et al,[7] we found no difference in mortality in childhood celiac disease according to follow-up time.

We examined mortality in 2 entities not previously studied: inflammation without villous atrophy and latent celiac disease. Mortality was highest in inflammation. In Sweden, individuals with celiac disease are treated with a gluten-free diet, while very few with inflammation are.[18] Those with inflammation may have an overall worse prognosis than those with villous atrophy, since institution of a gluten-free diet often leads to normalization of the mucosa. This excess risk, however, decreased over time and was identical to that in celiac disease after 5 years of follow-up. It could be that some individuals with inflammation had acute inflammation that healed spontaneously, driving the risk estimate toward 1.

Two recent studies[10,11] reported increased risk of death in individuals with positive celiac disease serology; neither of these studies examined the mucosa. Our risk estimate for mortality in latent celiac disease is similar to that of antibody-positive individuals in the study by Anderson et al[11] but lower than that of a German study of tTG-positive patients.[10] These studies[10,11] probably consist of a mix of individuals with normal and abnormal mucosa.

We found similar mortality in patients with latent celiac disease and with villous atrophy. However, only in latent celiac disease diagnosed in childhood was the increased HR for mortality statistically significant, and then it was based on only 6 deaths. We examined the causes of death in 4 of these cases, and only in 1 was death due to disease that has previously been linked to celiac disease (pneumonia[5]). Given that the other 3 causes of death were congenital disorders, the increased mortality in latent celiac disease may be due to celiac disease testing in individuals with severe comorbidity.

This study has some limitations. We cannot rule out that some individuals with inflammation were misclassified as having normal mucosa (latent celiac disease) or partial villous atrophy. This might have overestimated the HR for death in latent celiac disease but could also explain why individuals with partial villous atrophy were at a higher risk of death than those with subtotal/total villous atrophy. The difference in mortality between partial and subtotal/total villous atrophy could also be a chance finding. However, the reliability of Swedish pathologists is high. Earlier validation found that 96% of biopsies with normal mucosa and 90% of tissue samples with villous atrophy are correctly classified.[18] Risk of misclassification may be greater if histopathological examination is based on a single biopsy specimen, since villous atrophy and inflammation can be patchy.[28] Examining biopsy reports from 114 individuals with latent celiac disease, we found that, on average, these reports were based on 3 specimens.

In recent years, both the use of celiac disease serology and the awareness of celiac disease occurring in adults have increased. Although we cannot rule out that this has affected the likelihood of a biopsy, it does not seem to have affected mortality risk estimates. These were relatively constant over the period of the study and did not differ between individuals with celiac disease with and without serology. There is no risk of surveillance bias with regard to our outcome measure, as death was recorded independent of previous morbidity and treatment.

We used biopsy data to identify and define celiac disease. Others have used serology data to identify celiac disease,[11] but that approach has disadvantages. Even though the sensitivity of tTG is high in total villous atrophy, it decreases to about 70% in partial villous atrophy (also regarded as celiac disease) and is even lower in inflammation.[29] Since antibodies have only lately been introduced in clinical practice, a study based on antibody levels would have had short follow-up. Our use of biopsy data allows for longer follow-up and a chance to distinguish among normal mucosa, inflammation, and villous atrophy and even between partial and subtotal/total villous atrophy. While we found no difference in overall mortality in individuals with villous atrophy with and without celiac disease serology, we were unable to estimate HRs for patients with inflammation and positive celiac disease serology because of lack of data on celiac disease serology.

Biopsy samples without atrophy may be misinterpreted as atrophic if the samples are wrongly oriented, and villous atrophy may occur in other diseases than celiac disease. It could be argued that villous atrophy may not represent celiac disease. However, most other diagnoses with villous atrophy[28] are rare, and as part of the pilot work for this study, 2 independent reviewers manually examined biopsy reports in 1534 individuals with inflammation or villous atrophy where there were indications of comorbidity.[18] Only rarely was disease other than celiac disease mentioned in the small-intestinal biopsy reports (inflammatory bowel disease most commonly in 0.3%). Chart validation also found that 94.7% of biopsy reports with villous atrophy were consistent with clinical celiac disease.[18]

Some patients with inflammation may not have had celiac disease–related inflammation but instead nonspecific small-intestinal inflammation. Earlier research suggests that up to 40% of individuals with small-intestinal biopsy have gluten-sensitive enteropathy.[30] Given that clinical suspicion of celiac disease is the only major indication for small-intestinal biopsy in Sweden, we expect most individuals with inflammation to have early stage celiac disease. Patients with inflammation and celiac disease in

our study also had similar symptoms and signs. Comorbidity other than celiac disease was rare in inflammation in our validation study, with inflammatory bowel disease being most common in 1.6%.[18] Still, we cannot rule out that some patients with inflammation do not have celiac disease. The current study cannot determine if mortality in non–celiac disease–related inflammation differs from that of celiac disease–related small-intestinal inflammation.

We did not adjust for smoking. Smoking is negatively[31,32] or not at all[33] associated with celiac disease but positively associated with death. However, smoking is strongly linked to socioeconomic status and education in Sweden, and we adjusted all analyses for education, which did not influence estimates. We did not have access to weight and height data. Individuals with celiac disease have lower body mass index than controls. However, celiac disease and chronic inflammation are likely to induce malnutrition, suggesting that malnutrition is an intermediate in the causal pathway and not a true confounder. Another limitation of using registry data is that we cannot estimate mortality according to presence or absence of symptoms. In a subset of patients with celiac disease, 79% had gastrointestinal symptoms and 35% had anemia at diagnosis.[18]

There may be several explanations for the increased mortality seen in our cohorts. Malnutrition of energy and vitamins and chronic inflammation may increase the risk of death[12] (many patients with celiac disease have persisting duodenal lesions despite a gluten-free diet[34]). We cannot rule out that preexisting disease contributed to the overall increased risk of death.

In conclusion, we found increased HRs for death in individuals with biopsy-verified celiac disease, inflammation, and latent celiac disease, although absolute risks were small. Individuals undergoing small-intestinal biopsy in childhood had increased HRs for death. Cardiovascular disease and malignancy were the main causes of death in celiac disease.

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Study concept and design: Ludvigsson, Montgomery, Ekbom, Brandt.
Acquisition of data: Ludvigsson.
Analysis and interpretation of data: Ludvigsson, Granath.
Drafting of the manuscript: Ludvigsson, Montgomery, Ekbom, Granath.
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Statistical analysis: Ludvigsson, Granath.
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