



Published in final edited form as:

Aliment Pharmacol Ther. 2013 February ; 37(3): 332–339. doi:10.1111/apt.12164.

Mucosal Healing and Mortality in Celiac Disease

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Abstract

BACKGROUND AND OBJECTIVES—Celiac disease (CD), characterized by the presence of villous atrophy (VA) in the small intestine, is associated with increased mortality, but it is unknown if this excess mortality is influenced by mucosal recovery. We examined overall mortality according to mucosal recovery in CD.

METHODS—Through biopsy reports from all pathology departments (n=28) in Sweden we identified 7,648 individuals with CD (defined as VA) who had undergone a follow-up biopsy within 5 years following diagnosis. We then used Cox regression to examine overall mortality according to mucosal recovery in the follow-up biopsy (persistence of VA vs. recovery).

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Details of ethics approval: This project (2006/633-31/4) was approved by the Research Ethics Committee of the Karolinska Institute, Sweden on June 14th, 2006.

Competing interest statement

JAM: **Grant support:** Alba Therapeutics (>\$50,000); **Advisory board:** Alvine Pharmaceuticals, Inc. (<\$10,000), Nexpep (<\$10,000), **Consultant** (*none* above 10,000 USD): Ironwood, Inc., Flamentera, Actogenix, Ferring Research Institute inc., Bayer Healthcare Pharmaceuticals, Vysera Biomedical, 2G Pharma, Inc, ImmunosanT, Inc and Shire US Inc. (The other authors have no conflict of interest to declare).

A STROBE statement has been submitted as a separate file.

Author contributions:

ICMJE criteria for authorship read and met: BL, JFL, FG, AE, SMM, JAM, ART, PG.

Agree with the manuscript's results and conclusions: BL, JFL, FG, AE, SMM, JAM, ART, PG

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Supervised the project: JFL.

Obtained funding: JFL.

RESULTS—The mean age of CD diagnosis was 28.4, 63% were female, and the median follow-up after diagnosis was 11.5 years. Of the 7,648 patients, persistent VA was present in 3,317 (43%). There were 606 (8%) deaths. Patients with persistent VA were not at increased risk of death compared to those with mucosal healing (Hazard Ratio 1.01; 95% Confidence Interval 0.86-1.19). Mortality was not increased in children with persistent VA (HR 1.09 95% CI 0.37-3.16) or adults (HR 1.00 95% CI 0.85-1.18), including adults older than age 50 years (HR 0.96 95% CI 0.80-1.14).

CONCLUSION—Persistent VA was not associated with increased mortality in CD in this population followed for a median of 11.5 years. While a follow-up biopsy will determine if there is improvement in histology and allow detection of refractory disease in symptomatic patients, our study suggests that early routine follow up biopsies performed within 5 years does not predict long-term mortality risk.

Keywords

coeliac; death; inflammation; serial biopsy (British spelling of *coeliac*)

Introduction

Celiac disease (CD) is an immune-mediated disorder that occurs in approximately 1% of the Western world.¹⁻² In patients with CD, ingestion of gluten causes small intestinal inflammation and villous atrophy (VA). Typically, patients are recommended a gluten-free diet for life, and with dietary adherence most symptoms will usually resolve.

Patients with CD are at an increased risk of earlier death.³⁻⁴ The gluten-free diet may be responsible for the fact that the excess mortality observed in CD decreases towards that of the general population in the years following diagnosis.⁴

The diagnosis of CD is based on characteristic histopathologic abnormalities on small intestinal biopsy in the appropriate clinical context. A follow-up biopsy had earlier been considered standard-of-care to confirm healing after adoption of a gluten-free diet.⁵ However, subsequently this practice has declined due to the availability of serology data that normalize after elimination of dietary gluten.⁶ As a result, more recent guidelines no longer explicitly mandate a follow-up biopsy.⁷ Nevertheless, multiple studies of patients undergoing follow-up small intestinal biopsy have shown that persistent VA is observed in a large proportion of patients, as high as 62-79% in patients in the United States.⁸⁻⁹ Persistent VA is often present even in those patients with normalized serologies,⁸⁻¹² but is more commonly present in those whose adherence to the gluten-free diet is poor.^{9, 11-12}

It is unknown if survival in CD is related to mucosal recovery. An earlier study found that mucosal healing was associated with a decreased risk of death that did not achieve statistical significance, possibly due to inadequate power (241 patients, with 11 deaths).⁹ A second study of apparently asymptomatic individuals with persistent VA (n=13) reported high rates of malignancy and other morbidity associated with failure to heal.¹³ Both of these studies were limited by small size and potential for referral bias.

We therefore examined mortality in a Swedish nationwide cohort study of more than 7,000 patients with biopsy-verified CD and a follow-up biopsy.

Methods

Patients with CD were identified through biopsy reports from all (n=28) Swedish pathology departments. Using the unique personal identity number (PIN¹⁴), we matched biopsy data to the Total Population Register and the Swedish Cause of Death Register.

Collection of biopsy data

Collection of biopsy data has been described previously.^{4, 15} Between October 2006 and February 2008, we identified patients with CD through computerized biopsy reports from all of the 28 Swedish pathology departments.¹⁵ Of the 29,096 CD patients diagnosed between 1969 and 2008, 7,648 had undergone a follow-up biopsy between 0.5 and 5 years after the first diagnostic biopsy with VA (Marsh class 3).¹⁶ For patients with more than one follow-up biopsy, the earliest follow-up biopsy within the time period of 6 months to five years was included.

Classification of follow-up biopsies

Follow-up biopsies were *a priori* dichotomized into persistent VA (Marsh class 3: partial or subtotal-total VA) or improvement (Marsh class 0-2: normal mucosa or inflammation equaling intraepithelial lymphocytosis but without VA).¹⁶ Follow-up histology was determined by local pathologists. Earlier validation has shown that Swedish pathologists correctly classify 90% of samples with VA; further validation showed that patients with VA in this database accurately correlated with a clinical diagnosis of CD in 95% of cases.¹⁵

Mortality data—Through the Total Population Register,¹⁷ we were able to ascertain date of death among study participants. Cause-specific mortality was estimated through linkage with the Swedish Cause of Death Register,¹⁸⁻²⁰ a nationwide register since 1961. Cause-specific mortality was divided into the following four groups based on earlier research in CD: malignancy, cardiovascular disease, respiratory disease and other disease.²¹

Statistical analyses

We compared the survival of patients with persistent atrophy to those with mucosal healing using Cox proportional hazards. Follow-up began on the date of the follow-up biopsy. Follow-up ended on December 31, 2010, or earlier if the patient was lost to follow-up, emigrated, or died. We adjusted for the following covariates: age at follow-up biopsy, gender, time period, duration of disease (i.e. time elapsed between diagnosis of CD and follow-up biopsy), and educational attainment.

In a secondary analysis, we compared those who underwent follow-up biopsy to those who did not undergo follow-up biopsy, adjusting for the same covariates as above; follow-up time began on the date of diagnosis.

In preplanned sensitivity analyses, we redefined the window period of the follow-up biopsy. We repeated the Cox model restricting the analysis to three time windows, depending on the time elapsing between the diagnosis of CD and the follow-up biopsy: <1 year; 1 year to <3 years, and ≥ 3 years. Because multiple prior studies have demonstrated that the mortality risk associated with CD varies over time,^{4, 22} we tested the proportional hazards assumption by employing pseudo-time-dependent variables, and derived hazard ratios as a function of time since the follow-up biopsy. We tested for effect modification by introducing interaction terms in the Cox model, and tested their statistical significance via the Wald chi square test. For cause-specific mortality, follow-up ended on December 31, 2009 since this information was only available to this date.

Serological data

For a subset of patients, the results of anti-gliadin (AGA), anti-tissue transglutaminase (TTG), and anti-endomysial antibodies (EMA) were available. We obtained computerized data from serology reports and age-specific reference values in individuals undergoing a small intestinal biopsy at one of ten Swedish university hospitals (covering 49% of the Swedish population).¹⁵

In this subgroup analysis, we identified all patients who had a positive serological result (IgA or IgG) prior to, or within 6 months following, the histological diagnosis of CD. Among these patients, we further identified those who had additional serological testing within 6 months (before or after) their follow-up biopsy. We compared those who converted to seronegative status, to those who remained seropositive with regard to rates of persistent villous atrophy.

Statistical and Power analysis

We used the chi square test when comparing proportions of categorical variables, and the t test or Mann Whitney test when comparing continuous variables. We used a p value cutoff of <0.05 for statistical significance. All statistical calculations were performed using SAS version 9.2 (SAS Institute Inc, North Carolina).

In a post-hoc power analysis using a two-sided level of significance 0.05 and 80% power, we determined that our sample size would yield a minimally detectable relative risk of 1.27.

Ethics

The study was approved by the Research Ethics Committee of Karolinska Institutet, Stockholm, Sweden.

Results

There were 29,096 individuals in Sweden with biopsy-confirmed evidence of CD. Of these 29,096 patients, 9,725 (33%) had a follow-up biopsy. When defining the period of follow-up biopsy as those occurring at least 6 months and no more than 5 years after the initial diagnosis of CD, 7,648 (79% of all patients with >1 biopsy) were included for further analysis.

The mean age at diagnosis of the 7,648 patients was 28.4 years (median 25.0, SD 24.9), which was younger than the age of diagnosis for those individuals who did not have a follow-up biopsy (Table 1). Females comprised 63% of this group. The initial histopathology demonstrated partial VA in 12%, while the remainder had either subtotal/total VA (27%) or VA without further characterization (61%). The overall mortality rate of patients who underwent follow-up biopsy was slightly less than those patients with CD who did not undergo follow-up biopsy (Adjusted HR 0.88, 95% CI 0.80-0.96, p=0.0036).

Patients were followed for a median of 11.5 years from diagnosis, and 9.9 years after follow-up biopsy. For 1,927 patients, 25% of the cohort, observation time after follow-up biopsy exceeded 15 years. The median duration of CD at the time of follow-up biopsy was 1.3 years, with 26% of the cohort undergoing follow-up biopsy between 6 months and 1 year after diagnosis (1-2 years after diagnosis: 45%; and 2-5 years after diagnosis: 29%).

Follow-up biopsy demonstrated persistent VA in 3,317 patients, 43% of the cohort. Patients with partial VA on the initial diagnostic biopsy were less likely to have persistent VA on follow-up biopsy (30%) than those who originally had subtotal/total VA (42%, p<0.0001).

Serological status and mucosal healing

Among patients in whom serological results were available, 905 had a positive serology prior to the initial biopsy or within six months following the initial biopsy demonstrating CD (12% of the 7,648 patients who underwent follow-up biopsy).

Of these 905 seropositive patients, 545 (60%) had repeat serology assessments within 6 months of the second biopsy. Of these 545 patients with a follow-up biopsy and follow-up serology, 224 (41%) had a persistently positive serology. The proportion of patients with persistent villous atrophy was greater in those with persistently positive serology (139/224, 62%) than in those with conversion to negative serology (67/321, 21%, $p < 0.0001$).

Mucosal recovery and overall mortality

Of the 7,648 patients with a follow-up biopsy, 606 (8%) died during the observation period. Persistent VA was associated with an increased risk of death in this unadjusted analysis (Log rank test by chi square 14.3, $p < 0.0001$). On unadjusted Cox proportional hazard modeling, persistent VA was associated with an increased risk of death (HR 1.37 95% CI 1.16-1.62).

Adjusted Cox proportional hazards are shown in Table 2. Persistent VA was no longer associated with mortality after adjusting for age at follow-up biopsy, gender, calendar period of diagnosis, educational attainment, and duration of CD (HR 1.01 95% CI 0.86-1.19). This null association was present in adults (HR 1.00 95% CI 0.85-1.18) as well as children (HR 1.09 95% CI 0.37-3.16).

Increased age and male gender were independently associated with mortality. However, age did not modify the null association between persistent VA and mortality (p value for interaction term 0.1284), nor did gender (p value for interaction term 0.9960). The null association between persistent villous atrophy and mortality was seen in both men (HR 1.00 95% CI 0.79-1.26) and women (HR 1.01 95% CI 0.80-1.28). Risk estimates were similar in patients aged ≥ 50 years at the time of follow-up biopsy (HR 0.96 95% CI 0.80-1.14).

Mortality risk was not significantly increased in the three pre-specified time period strata after follow-up biopsy (6 months to 1 year: HR 0.82 95% CI 0.48-1.38; 1-5 years HR 0.87 95% CI 0.65-1.17; greater than 5 years HR 1.12 95% CI 0.91-1.39).

Redefining the time windows of follow-up biopsy did not influence the relationship between persistent VA and mortality (Table 3).

Serological status and mortality

In the subset of patients with baseline and follow-up serologies, 224 patients had persistent positive serologies, and there were 15 deaths. On multivariate Cox analysis, the HR for persistent positive serology (adjusting for other covariates including persistent villous atrophy) was 3.17 (0.8-12.6, $p = 0.1006$), while the HR for persistent villous atrophy was 2.05 (0.56-7.34, $p = 0.2772$).

Mucosal recovery and cause-specific mortality

Persistent VA on follow-up biopsy was not associated with an increased risk of death from cardiovascular, neoplastic, respiratory, or other causes (Table 4).

Discussion

In this nationwide population-based study we found no association between mucosal healing and death rates in patients with CD when followed for a median of 11.5 years after diagnosis and 9.9 years after follow-up biopsy. This null association was similar for adults (HR 1.00 95% CI 0.85-1.18) as well as children (1.09 95% CI 0.37-3.16). This mortality estimate remained stable when defining the time frame for follow-up biopsy, and it remained unchanged in multiple time strata after follow-up biopsy.

This is the first study with adequate power to assess the mortality risk in patients with CD who undergo follow-up biopsy. Prior studies have suggested that patients with persistent VA were at risk for adverse outcomes.^{9,13}

Our finding of no increased mortality risk among patients with CD and persistent VA was hence unexpected, given the prior literature. Earlier studies suggesting a possible mortality risk may have been subject to selection bias, given their single-center settings.

A prior study of this cohort found that after the first year of follow-up, the risk of death for patients with CD was the same as those with “latent CD,” as defined by positive serology but normal small intestinal histology (HR for CD 1.26 95% CI 1.20-1.32; HR for latent CD 1.27 95% CI 1.02-1.52). Since the mortality risk for those with mucosal healing would not likely be lower than those with latent CD (who have normal histology on their first biopsy), and since patients with latent CD have the same mortality risk as those with CD, one might therefore surmise that mucosal healing would not be associated with a decreased mortality. Our results indicate that the results of the follow-up biopsy do not further risk-stratify patients with regard to mortality. Although persistent VA may reflect imperfect adherence to the gluten-free diet,^{9, 11-12, 23-24} it may alternatively indicate variable rates of healing; prior studies of patients undergoing serial biopsy have shown that a substantial proportion of patients with persistent VA on initial follow-up biopsy demonstrate healing on subsequent biopsy.^{9, 25} Another possible explanation for the null association between persistent villous atrophy and mortality is that any potential increase in mortality related to malabsorption or activated autoimmunity is offset by a protective effect; for example, patients with CD have a decreased risk of breast, ovarian, and endometrial cancer, which is likely related to lower adiposity and early menopause.²⁶

The proportion of patients with persistent VA was 43%, which falls within the range reported previously.^{8, 10-12, 25, 279, 23-24} Most studies have reported rates of persistent VA to be between 20% and 50%.^{10-11, 24-25, 27} Our results confirm that persistent VA is common, but also indicate that this finding is not associated with increased mortality. Other clinically relevant outcomes possibly associated with a histological response to the gluten-free diet were not investigated in this study, such as quality of life, bone density or the development of further autoimmune diseases.²⁸ Thus, mucosal healing and its confirmation may still be desirable after treatment with a gluten-free diet in patients with CD.

This study has a number of strengths. In this population-based study we were able to link data on follow-up biopsies in patients with CD from 28 pathology departments to mortality data from Swedish National Registers. A separate validation study involving the review of more than 1,500 charts demonstrated the accuracy of using these diagnosis codes for identification of CD patients in this database.¹⁵ During the follow-up of 7,648 patients there were more than 600 deaths, giving this study unprecedented power to examine not only overall mortality, but mortality in important subgroups such as children, and mortality by calendar period. The Cause of death Register includes 99.7% of all Swedish death causes, and linkage through the unique personal identity number guarantees a virtually 100% follow-up.¹⁴ Unlike previous estimates of morbidity and mortality associated with

histopathological follow-up, this population-based study is not subject to referral bias, or loss to follow-up with regard to mortality. The subgroup analysis that included patients with serological information corroborates prior studies that found a correlation between persistently elevated serology results and persistent villous atrophy.^{9, 11-12}

This study has several limitations. Despite the population-based source of sampling, selection bias is a possibility; we had data on follow-up biopsy in 7,648, 26% of the 29,096 patients with CD. Swedish data suggest that follow-up biopsies in children were more common in the 1990s and in the early years after the year 2000.²⁹ As this cohort of patients who underwent follow-up biopsy is younger than that the overall CD cohort (mean age at diagnosis 28.4 versus 33.4, $p < 0.0001$), it is possible that the overall exposure to gluten in this group was relatively low, leading to a low mortality rate. When we restricted this population analysis to those aged ≥ 50 years, the null results persisted.

When assessing whether patients undergoing follow-up biopsy were characteristically different to those not being biopsied a second time (Table 1), we found a slightly lower mortality rate in patients undergoing a second biopsy (HR 0.88, 95% CI 0.80-0.96). This raises concern regarding selection bias. One might have supposed that patients undergoing follow-up biopsy might do so due to clinical worsening; these results suggest that, in fact, these follow-up biopsies were likely done as part of routine care. The modest protective effect may reflect a greater tendency to adhere to medical follow-up.

The patients in this population-based study are likely representative of CD patients across the clinical spectrum of severity. While the “Swedish CD epidemic”³⁰ increased the awareness of CD among Swedish physicians, there has only been one major CD screening initiative in Sweden so far (the ETICS study).³¹ Although that study identified 145 asymptomatic patients with CD, these patients would constitute less than 0.5% of the total population of our original cohort of 29,096 patients with CD⁴ and have little influence on the risk of complications including death. In a random subset of CD patients,¹⁵ 51% of patients (60/118) had severe CD defined as having either weight loss/growth failure, diarrhea or both. This compares to 55% of patients in an Italian cohort of CD patients,³² while 65% of American CD patients in our earlier paper on follow-up mortality had “classical CD.”⁹

The time period allowable between CD diagnosis and follow-up biopsy was 6 months to 5 years; this cut-off was used so as to minimize the possibility that follow-up biopsy was prompted by clinical worsening. In a sensitivity analysis, changing the time period of the second biopsy inclusion criteria did not change our results (Table 3).

Misclassification is unlikely to be substantial in this analysis. In one center, Örebro, the misclassification rate (i.e. biopsy was not a routine follow-up biopsy but was rather prompted by a new clinical development) was 6.7% (7/105). We had data on the number of biopsy specimens in 65 of remaining 98 individuals, and the mean number of specimens submitted was 3.6.³³

Another limitation is the lack of comprehensive information data on dietary adherence in every patient. Earlier evidence suggests that questioning for symptom response to a gluten-free diet correlates well with intestinal damage.¹² However, data from our own research group has indicated that dietary adherence does not always lead to mucosal recovery.⁸ When we reviewed the charts of 121 randomly selected patients with VA,¹⁵ 22 patients had data on adherence and a follow-up biopsy. All 4 patients with poor dietary adherence had persistent VA, but of 18 with reportedly good dietary adherence, 7 (39%) nevertheless had persistent VA on their follow-up biopsy ($p = 0.090$). While persistent villous atrophy was greater in those with positive follow-up serologies, up to 21% with negative follow-up serologies had

persistent villous atrophy, consistent with prior reports.⁸⁻¹² Accurate and non-invasive tests to predict mucosal healing are needed.

As we lacked data on adherence to the gluten free diet, it is possible that persistent villous atrophy on the follow-up biopsy may have prompted improved dietary adherence, leading to a null mortality finding. However, this is unlikely to be the case; if it were, we would expect there to be a varying mortality risk after the second biopsy (i.e. an elevated hazard ratio in the earliest time stratum, followed by a null finding in later time strata). When we performed the mortality analysis according to time after the second biopsy, there was no heterogeneity of risk according to time.

Among patients with persistent VA in the control biopsy, there may be some patients with refractory CD. Given the high excess mortality in Refractory CD,³⁴⁻³⁶ our data suggest that refractory CD is uncommon in a non-selected population since it would otherwise have affected the mortality risk in this study.

Despite the null result, it remains possible that mortality increases over a longer term follow-up period. The patients in this study were followed for a median of 11.5 years after diagnosis, and 9.9 years after follow-up biopsy. We therefore cannot completely rule out a long-term effect on mortality among those with persistent VA. To address limitation we derived separate hazard ratios as a function of time since the follow-up biopsy (see Results section), and found no association between persistent VA and mortality in the long-term time strata.

We conclude that there is no association between the histopathologic appearance of follow-up biopsy and mortality risk in patients with CD when followed for a median of 11.5 years after diagnosis and 9.9 years after follow-up biopsy. The excess mortality reported in CD is not a consequence of persistent VA, and routine follow-up biopsy for this purpose may not be necessary. Future studies are warranted to assess the role in follow-up biopsy in predicting subsequent morbidity in celiac disease.

Acknowledgments

BL: The American Scandinavian Foundation, the Celiac Sprue Association, and the National Center for Research Resources, a component of the National Institutes of Health (KL2 RR024157).

AE: Stockholm County Council.

JAM: The National Institutes of Health – DK071003 and DK057892.

JFL: Örebro University Hospital, Karolinska Institutet, the Swedish Society of Medicine, the Swedish Research Council – Medicine (522-2A09-195) and the Swedish Celiac Society.

The funders did not influence the study design, the analyses or the decision to submit the paper.

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What is current knowledge?

- Patients with celiac disease are at increased risk of death
- Also individuals with a normal mucosa but positive celiac disease serology are at increased risk of death
- Some data suggest that poor dietary adherence influence the risk of death in celiac disease

What is new here?

- Persistent villous atrophy did not influence the risk of death in celiac disease.
- Persistent villous atrophy did not influence the risk of cause-specific death such as death from cardiovascular disease, malignancy or respiratory disease.
- Routine follow up biopsies performed within 5 years does not predict long-term mortality risk.

Table 1

Characteristics of patients who did and did not undergo follow-up small intestinal biopsy 6 months to 5 years after initial diagnosis of CD.

Characteristic	Follow-up biopsy (n=7,648)	No follow-up biopsy (n=19,371)	p value
Age at diagnosis (mean/median years)	28.4/25	33.4/32	<0.0001
Gender [n (%)]			
Male	2,816 (37)	7,531 (39)	0.0017
Female	4,832 (63)	11,840 (61)	
Calendar period of diagnosis [n (%)]			<0.0001
1989	1,074 (14)	2,409 (12)	
1990-1999	3,274 (43)	7,610 (39)	
2000	3,300 (43)	9,352 (48)	
Index biopsy result [n (%)]			0.0442
Partial villous atrophy	925 (12)	2,415 (12)	
Subtotal/total VA	2,055 (27)	4,921 (25)	
Non-specified VA	4,668 (61)	12,035 (62)	
Duration of diagnosed CD at the time of repeat biopsy [n (%)]			
0.5-1 year	2,024 (26)	--	--
Between 1 and 2 years	3,429 (45)		
2-5 years	2,195 (29)		
Died during follow-up [n (%)]	606 (8)	2,669 (14)	<0.0001

Table 2

Cox proportional hazard model assessing the association of persistent histologic activity with mortality rate.

Characteristic	Adjusted* Hazard Ratio (95% CI)	p value
Result of follow-up biopsy		
Mucosal healing	1.0 (reference)	(reference)
Villous atrophy	1.01 (0.86-1.19)	0.9208
Age at follow-up biopsy		<0.0001
0-2	0.03 (0.01-0.07)	
3-9	0.01 (0.004-0.04)	
10-19	0.14 (0.07-0.3)	
20-29	0.12 (0.05-0.28)	
30-39	0.19 (0.11-0.33)	
40-49	0.55 (0.39-0.78)	
50-59	1.0 (reference)	
60-69	2.65 (2.02-3.47)	
70-79	7.47 (5.76-9.68)	
80	16.64 (11.48-24.13)	
Gender		<0.0001
Male	1.85 (1.57-2.17)	
Female	1.0 (reference)	
Calendar period of diagnosis		0.0483
1989	1.0 (reference)	
1990-1999	1.04 (0.82-1.33)	
2000	0.80 (0.59-1.08)	
Education level		0.0031
< 2 years of high school	1.0 (reference)	
2 years of high school	0.85 (0.68-1.06)	
3 years of high school	0.69 (0.50-0.95)	
College/University	0.72 (0.55-0.93)	
Unknown	1.37 (1.02-1.86)	
Duration of diagnosed disease prior to 2 nd biopsy		0.2184
0.5-1 year	1.0	
Between 1 and 2 years	0.96 (0.79-1.16)	
2-5 years	1.15 (0.94-1.40)	

* Adjusted for age at follow-up biopsy, gender, time period, duration since diagnosis, and educational attainment.

Table 3

Mortality risk, redefining follow-up biopsy window (all the same covariates as previous, except for disease duration)

Follow-up biopsy definition	Adjusted* Hazard Ratio for persistent villous atrophy (95% CI)	p value
6 months - 1 year after diagnosis (n=2,024)	1.30 (0.98-1.72)	0.0704
Between 1 and 3 years after diagnosis (n=4,575)	0.93 (0.73-1.19)	0.5832
Year 3-5 after diagnosis (n=1,049)	0.74 (0.48-1.14)	0.1766

* Adjusted for same covariates as Table 2.

Table 4

Association of follow-up biopsy result with cause-specific mortality

Cause-specific mortality	Adjusted* Hazard Ratio for persistent villous atrophy (95% CI)	p value
Cardiovascular	1.03 (0.76-1.38)	0.8712
Malignancy	1.20 (0.88-1.66)	0.2542
Respiratory	0.78 (0.41-1.48)	0.4427
Other	0.94 (0.69-1.29)	0.7117

* Adjusted for same covariates as Table 2.