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# **Persistent mucosal damage and the risk of epilepsy in people with celiac disease**

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## ABSTRACT

**Background:** Celiac disease (CD) is associated with an increased risk of developing epilepsy, a risk that persists after CD diagnosis. A significant proportion of CD patients have persistent villous atrophy (VA) on follow-up biopsy. This study's objective was to determine whether persistent VA on follow-up biopsy affects long-term epilepsy risk and epilepsy-related hospital emergency admissions.

**Methods:** Nationwide Cohort Study. We identified all people in Sweden with histological evidence of CD who underwent a follow-up small intestinal biopsy (1969-2008). We compared those with persistent VA to those who showed histological improvement, assessing the development of epilepsy and related emergency hospital admissions (defined according to relevant ICD codes in the Swedish Patient Register). Cox regression analysis was used to assess outcome measures.

**Results:** Of 7590 people with CD who had a follow-up biopsy, VA was present in 43%. The presence of persistent VA was significantly associated with a reduced risk of developing newly-diagnosed epilepsy (hazard ratio [HR] 0.61; 95% confidence interval [CI] 0.38–0.98). On stratified analysis this effect was primarily amongst males (HR 0.35; 95 CI 0.15–0.80). Among the 58 CD patients with a prior diagnosis of epilepsy, those with persistent VA were less likely to visit an emergency department with epilepsy (HR 0.37; 95%CI 0.09-1.09).

**Conclusions:** In a population-based study of CD individuals, persisting VA on follow up biopsy was associated with reduced future risk of developing epilepsy but did not influence emergency epilepsy-related hospital admissions. Mechanisms as to why persistent VA confers this benefit requires further exploration.

## INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy, which has a prevalence of 1% in Western populations.[1, 2] It occurs in genetically susceptible individuals following exposure to dietary gluten. Strict adherence to a gluten-free diet (GFD) is the mainstay of treatment, which can reduce the risk of complications such as lymphoma, osteoporosis and micronutrient deficiencies.[3]

Neurological conditions such as cerebellar ataxia,[4] peripheral neuropathy,[5] and headache[6] are all recognised extraintestinal manifestations associated with CD. Another important neurological disorder that has been examined is epilepsy. Previous work has shown large variability in the prevalence and incidence of epilepsy in CD (0-7.2%),[7-9] with our previous population-based study demonstrating a moderately increased risk (HR =1.42; 95% confidence interval [CI] = 1.24–1.62).[10] Potential underlying pathophysiological mechanisms for this association have been described previously in children in celiac disease, epilepsy and cerebral calcifications (CEC) syndrome, however uncertainty exists about these exact mechanisms in adults.[11]

Follow-up biopsy has emerged as a potentially important approach to risk-stratify CD patients with regards to long-term prognosis. The rates of persistent villous atrophy (VA) are variable in the literature, occurring in > 30% of CD patients in most series,[12-14] with persisting VA inversely correlating with GFD adherence.[13, 15, 16] Although persistent VA does not impact overall mortality in CD, it may influence morbidity and be a factor explaining heterogeneity in previous epilepsy and CD studies.[17]. Performing a follow-up biopsy was historically considered standard-of-care to confirm healing after adoption of a gluten-free diet.[18] However, the practice has subsequently declined due to the availability of serology data, which normalizes after elimination of dietary gluten.[19] This had led to recent guidelines no longer explicitly mandating a follow-up biopsy.[2, 20]

The study examines whether persistent VA, as compared with mucosal healing is associated with an increased risk of developing newly diagnosed epilepsy among people with CD. In addition, we explore whether mucosal healing influences future epilepsy-related hospital emergency admissions in those with known epilepsy at the time of follow-up biopsy.

## **METHODS**

### *Identification of individuals with CD*

During the years 2006–2008 we queried all pathology departments in Sweden (n = 28) for reports of VA, as identified by SnoMed codes. Details regarding this database have been published previously.[21] In brief, VA was identified by Swedish pathologists and a prior validation study demonstrated that among individuals identified via these histology codes, a clinical diagnosis of CD was present in 95%; alternative/comorbid diagnoses were rare (with inflammatory bowel disease, the most common comorbidity, present in 0.3% of 1,534 manually reviewed patient records).[21]

The individuals in this analysis are those with CD who underwent more than one duodenal biopsy; they therefore represent a subset of all CD patients, who were included in our earlier study that found an increased risk of epilepsy in CD.[10] We identified those people with CD who underwent follow-up biopsy between 6 months and 5 years after initial CD diagnosis. Those who had a modified Marsh histopathology score[22] of 3 were classified as having persistent VA, while those with a less severe score were classified as healed. As reported previously, among a subset of patients where serologic data was available, villous atrophy was more common among those with persistently elevated celiac disease serologies (62%) compared to those with serologic normalization (21%).[17]

### *Identification of individuals with Epilepsy and hospital emergency admissions*

Epilepsy was defined according to relevant International Classification of Diseases (ICD) codes in the Swedish National Patient Register[23]; our definition of epilepsy did not include status epilepticus or febrile convulsions (ICD-7: 353 except for 353.2; ICD-8: 345 except for 345.2; ICD-9: 345 except for 345Q; ICD-10: G40). The Swedish National Patient Register includes inpatient diagnoses from parts of Sweden since 1964 (nationwide since 1987), as well as hospital-based outpatient care since 2001. Emergency hospital admissions for epilepsy were defined also using relevant ICD codes in the Swedish Patient Register for epilepsy but also including status epilepticus (ICD-8: 345.2; ICD-9: 345Q, and ICD-10: G41) in patients with an earlier diagnosis of epilepsy.

### *Statistical considerations*

We used Cox proportional hazard models to compare the risk of developing epilepsy among those with persistent VA versus those with mucosal healing on follow-up biopsy. In this analysis, the observation time (i.e., time at risk) started on the day of the follow-up biopsy and ended on the date of developing epilepsy, death, emigration or December 31, 2009, whichever occurred first. In this analysis we chose a priori the following covariates in the model: age at follow-up biopsy, gender, duration of CD at the time of follow-up biopsy, educational attainment (or in the case of children the highest educational attainment between the parents) and calendar period of follow-up biopsy.

Because the risk of sequelae in CD (including mortality and morbidity) changes over time,[24] we tested the proportional hazards by recalculating the association between VA and the development of epilepsy during the following 3 pre-specified time strata: <1 year, 1–5 years, and >5 years after the patient's follow-up biopsy. We then performed stratified analysis by age,

gender, and calendar period of follow-up biopsy.

Analysis of emergency hospital related admissions for epilepsy was undertaken using Cox proportional hazard models. This analysis included all patients who were known to already have epilepsy at the time of follow-up biopsy. In addition to a Cox model measuring the risk of any emergency visit for epilepsy, we also assessed the association between persistent VA and the rate of emergency department visits among these individuals in the five years following their follow-up biopsy. For this latter model we calculated rate ratios using Poisson regression among patients with known epilepsy at the time of their follow-up biopsy who had at least 5 years of observation time after that date.

We used SAS version 9.3 (Cary, NC) for statistical analyses. We report risk estimates as hazard ratios (HR) and corresponding 95% confidence intervals (CI). All reported p values are two-sided. This study was approved by the Research Ethics Committee of the Karolinska Institute on June 14th, 2006. According to the board's decision no study participant was contacted as the study is strictly register-based.[25]

## **RESULTS**

### *Characteristics of patients who underwent follow-up biopsy*

Of 29,096 people with CD, 7648 (26%) underwent a follow-up biopsy between 6 months and 5 years after their initial CD diagnosis. 58 of these individuals were known to have epilepsy at the time of follow up biopsy, leaving 7,590 remaining (Table 1). The median (interquartile range) age of CD diagnosis was 25 (3– 51) years and the median (interquartile range) age of follow-up biopsy was 26.8 (5–52) years. Nearly half of the patients (45%) were younger than 20 years at

the time of follow-up biopsy. Most patients (63%) were female and 45% of patients had follow-up biopsy between 1 and 2 years after the CD diagnosis. A previous analysis of this cohort found that those CD patients who had a follow-up biopsy differed slightly from those who did not; they were diagnosed with CD at a younger age (mean 28.4 vs 33.4 years,  $P < 0.0001$ ), and had a slightly greater female predominance (63% vs 61%,  $P = 0.0017$ ).[17]

Patients were followed up for a median (interquartile range) of 8.9 (5.4–14.1) years after follow-up biopsy. Most patients (53%) had a follow-up biopsy after the year 2000. Of the 7,590 people who did not have epilepsy at the time follow-up biopsy, 3295 (43%) had persistent VA.

### *Risk of developing Epilepsy*

There were 75 new diagnoses of epilepsy during the observation period after follow-up biopsy. The mean/median (SD) time from follow-up biopsy to epilepsy diagnosis in these patients was 7.1/6.2 (5.5) years. Quantifications of the association between persistent VA and epilepsy stratified by gender, age, and calendar period are shown in Table 2. Persistent VA was associated with a reduced risk of developing epilepsy (HR 0.61; 95% CI 0.38–0.98), as compared to those with mucosal healing. This effect was primarily among males (HR 0.35; 95% CI 0.15–0.80) and there was no significant association between persistent VA and epilepsy among females (HR 0.85; 95% CI 0.46–1.57). To test the robustness of our results a sensitivity analysis was performed using patients that had at least 2 interactions with Swedish health care due to a diagnosis of epilepsy. This demonstrated similar results (HR 0.57; 95% CI 0.33–1.01), however findings were just short of statistical significance ( $p = 0.0532$ ). The low number of events for “partial” and “generalized-other” epilepsy subtypes in our cohort precluded any analysis using epilepsy subtypes.

On time-stratified analysis, the reduced risk of epilepsy was most pronounced in the first year after follow-up biopsy (HR 0.36; 95% CI 0.07–1.74), though this was not statistically significant.

The point estimates for the subsequent time strata were similar to each other (1-5 years: HR 0.66; >5 years: HR 0.64). A test for heterogeneity did not find that these three risk estimates differed significantly between time strata ( $p=0.78$ ).

#### *Persistent VA and Epilepsy related emergency hospital admissions*

58 people with CD had an established diagnosis of epilepsy at the time of follow up biopsy.

Those with persistent VA were less likely to visit an emergency department with epilepsy related problems, although not meeting statistical significance (HR 0.37; 95% CI 0.09-1.09,  $p=0.1605$ ).

When examining the rate of emergency department visits for epilepsy over a 5-year period, we identified 37 patients with a previous diagnosis of epilepsy who had 5 years of follow-up observation time. Among those with mucosal healing, the mean number of emergency visits over 5 years was 0.57, compared to 0.44 among those with persistent VA (Rate ratio for those with persistent VA compared to those with healing 0.51; 95%CI 0.13-2.02).

## **DISCUSSION**

In this population-based database of people with CD who underwent a follow-up biopsy, there was a reduced risk of developing epilepsy among those with persistent VA compared to those with mucosal healing. This finding was primarily amongst males. No significant difference in emergency hospital admissions for epilepsy was identified in those with persistent VA.

These findings contrast our original hypothesis. We had hypothesized that persistent VA would be associated with an increased risk of future epilepsy and influence hospital admissions. This hypothesis was based on the observation that CD patients develop epilepsy at a greater rate than would be expected in the general population.[10] It seemed plausible that the autoimmune

reaction inherent to CD would also increase epilepsy risk, with intestinal permeability potentially influencing blood-brain barrier permeability as has been reported in other neurological disorders.[26, 27] However, our findings suggest the mechanisms of mucosal injury and the chronic inflammation may be protective to developing epilepsy. TNF-alpha and the neuropeptide Ghrelin are two inflammatory mediators in CD that could have influenced outcomes. [28, 29] TNF-alpha is recognised to inhibit seizures in mice and Ghrelin has been shown to have anticonvulsant properties, which could have conferred protection to those not achieving mucosal healing.[30, 31]

An alternative explanation is that a diagnosis of epilepsy is more frequently sought out and detected amongst those with mucosal healing, who better adhere to a GFD. It may be that individuals who follow physician's advice in this regard are more likely to seek medical attention for minor symptoms (including possible convulsions/epilepsy), when compared to non-adherent individuals (with persistent VA) who may defer consultations. Other factors may also have influenced outcomes. Previous work has shown that although adhering to a GFD can induce mucosal healing, it can lead to an increase in body weight.[32, 33] As weight change has been shown to influence other conditions such as breast cancer and type 2 diabetes, it may be that that weight gain is adversely influencing neurological processes and inflammation.[34-36]

Another possibility is that patients with persistent VA on a first follow-up biopsy may not reflect long-term mucosal healing rates. In a study of patients undergoing serial small intestinal biopsy, the prevalence of mucosal healing was greater at 5 years (66%) than at 3 years (34%), suggesting that some individuals gradually heal over subsequent years.[15] In this population-based study, the prevalence of persistent VA was similar among those whose follow-up biopsy was performed 1–2 years after diagnosis and 2–5 years after diagnosis[37], suggesting that gradual mucosal

healing is not a widespread phenomenon at least within this timeframe. Another potential explanation is that patients undergoing follow-up biopsy may represent a healthier subset of patients with CD compared to those who did not, which may have been deferred due to medical comorbidities. Supporting this notion is our previously reported finding that overall mortality risk of individuals who underwent follow-up biopsy was slightly lower than those who did not have follow-up biopsy.[17] Although our study population had a large proportion of adults, the results were similar in both children and adult populations. These findings could suggest a shared underlying pathological mechanism between epilepsy and CD in both groups.

This is the first study to our knowledge investigating the risk of epilepsy according to follow-up histology in CD. This study has several strengths, including its population-based design and the independent ascertainment of cases from national health registers. The Swedish National Patient Register has been validated repeatedly, and the majority of diagnoses have a high positive predictive value (85–95%).[23] Furthermore, CD was identified through biopsy records showing VA. During the study period, biopsy remained the gold standard for diagnosis in both children and adults, and  $\geq 96\%$  of all pediatricians and gastroenterologists in Sweden reported performing a small intestinal biopsy before diagnosis.[21] A patient chart review found that 95% of all samples with VA represented CD, a higher positive predictive value than physician-assigned diagnosis for CD in the Swedish National Patient register.[38] In addition, VA in Sweden is rarely explained by diagnoses other than CD (0.3% of individuals with VA had inflammatory bowel disease).[21] Although positive CD serology was not included within the definition of CD, it has been demonstrated that 88% of those with available CD serology data have positive antibodies at the time of first biopsy.[21]

This study is limited by a lack of data regarding several important risk factors for epilepsy including previous head trauma, central nervous system infections and tumours.[39] Our ability

to determine risk factors for both of CD and epilepsy was limited to ascertainment of age, gender, and histological outcomes. We therefore could not adjust for the previously highlighted risk factors that could have influenced our results. Our analysis of emergency department visits was limited by the small number of patients who developed epilepsy prior to follow-up biopsy, raising the possibility that we had insufficient power to detect whether healing is associated with this outcome.

In conclusion, this analysis of more than 7,000 patients with CD undergoing follow-up biopsy found that persistent VA was associated with a significant reduction in subsequently developing epilepsy. Future work should investigate novel biomarkers of inflammation in CD that may impact epilepsy risk.

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## REFERENCES

- [1]. Mustalahti K, Catassi C, Reunanen A, *et al.* The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. *Ann Med.* 2010 **42**: 587-595.
- [2]. Ludvigsson JF, Bai JC, Biagi F, *et al.* Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. *Gut.* 2014 **63**: 1210-1228.
- [3]. Mooney PD, Hadjivassiliou M, Sanders DS. Coeliac disease. *BMJ.* 2014 **348**: g1561.
- [4]. Hadjivassiliou M, Sanders DS, Woodroffe N, Williamson C, Grunewald RA. Gluten ataxia. *Cerebellum.* 2008 **7**: 494-498.
- [5]. Ludvigsson JF, Olsson T, Ekbom A, Montgomery SM. A population-based study of coeliac disease, neurodegenerative and neuroinflammatory diseases. *Aliment Pharmacol Ther.* 2007 **25**: 1317-1327.
- [6]. Lionetti E, Francavilla R, Pavone P, *et al.* The neurology of coeliac disease in childhood: what is the evidence? A systematic review and meta-analysis. *Dev Med Child Neurol.* 2010 **52**: 700-707.
- [7]. Cakir D, Tosun A, Polat M, *et al.* Subclinical neurological abnormalities in children with celiac disease receiving a gluten-free diet. *J Pediatr Gastroenterol Nutr.* 2007 **45**: 366-369.
- [8]. Ruggieri M, Incorpora G, Polizzi A, Parano E, Spina M, Pavone P. Low prevalence of neurologic and psychiatric manifestations in children with gluten sensitivity. *J Pediatr.* 2008 **152**: 244-249.
- [9]. Zelnik N, Pacht A, Obeid R, Lerner A. Range of neurologic disorders in patients with celiac disease. *Pediatrics.* 2004 **113**: 1672-1676.
- [10]. Ludvigsson JF, Zingone F, Tomson T, Ekbom A, Ciacci C. Increased risk of epilepsy in biopsy-verified celiac disease: a population-based cohort study. *Neurology.* 2012 **78**: 1401-1407.
- [11]. Gobbi G. Coeliac disease, epilepsy and cerebral calcifications. *Brain Dev.* 2005 **27**: 189-200.

- [12]. Sharkey LM, Corbett G, Currie E, Lee J, Sweeney N, Woodward JM. Optimising delivery of care in coeliac disease - comparison of the benefits of repeat biopsy and serological follow-up. *Aliment Pharmacol Ther.* 2013 **38**: 1278-1291.
- [13]. Lanzini A, Lanzarotto F, Villanacci V, *et al.* Complete recovery of intestinal mucosa occurs very rarely in adult coeliac patients despite adherence to gluten-free diet. *Aliment Pharmacol Ther.* 2009 **29**: 1299-1308.
- [14]. Pekki H, Kurppa K, Maki M, *et al.* Performing routine follow-up biopsy 1 year after diagnosis does not affect long-term outcomes in coeliac disease. *Aliment Pharmacol Ther.* 2017 **45**: 1459-1468.
- [15]. Rubio-Tapia A, Rahim MW, See JA, Lahr BD, Wu TT, Murray JA. Mucosal recovery and mortality in adults with celiac disease after treatment with a gluten-free diet. *Am J Gastroenterol.* 2010 **105**: 1412-1420.
- [16]. Ciacci C, Cirillo M, Cavallaro R, Mazzacca G. Long-term follow-up of celiac adults on gluten-free diet: prevalence and correlates of intestinal damage. *Digestion.* 2002 **66**: 178-185.
- [17]. Lebowhl B, Granath F, Ekbom A, *et al.* Mucosal healing and mortality in coeliac disease. *Aliment Pharmacol Ther.* 2013 **37**: 332-339.
- [18]. Ciclitira PJ, King AL, Fraser JS. AGA technical review on Celiac Sprue. American Gastroenterological Association. *Gastroenterology.* 2001 **120**: 1526-1540.
- [19]. Rostom A, Dube C, Cranney A, *et al.* The diagnostic accuracy of serologic tests for celiac disease: a systematic review. *Gastroenterology.* 2005 **128**: S38-46.
- [20]. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA, American College of G. ACG clinical guidelines: diagnosis and management of celiac disease. *American Journal of Gastroenterology.* 2013 **108**: 656-676; quiz 677.
- [21]. Ludvigsson JF, Brandt L, Montgomery SM, Granath F, Ekbom A. Validation study of villous atrophy and small intestinal inflammation in Swedish biopsy registers. *BMC Gastroenterol.* 2009 **9**: 19.

- [22]. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. *Eur J Gastroenterol Hepatol*. 1999 **11**: 1185-1194.
- [23]. Ludvigsson JF, Andersson E, Ekbom A, *et al*. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011 **11**: 450.
- [24]. Ludvigsson JF, Montgomery SM, Ekbom A, Brandt L, Granath F. Small-intestinal histopathology and mortality risk in celiac disease. *JAMA*. 2009 **302**: 1171-1178.
- [25]. Ludvigsson JF, Haberg SE, Knudsen GP, *et al*. Ethical aspects of registry-based research in the Nordic countries. *Clin Epidemiol*. 2015 **7**: 491-508.
- [26]. Greco A, Rizzo MI, De Virgilio A, *et al*. Autoimmune epilepsy. *Autoimmun Rev*. 2016 **15**: 221-225.
- [27]. Jackson JR, Eaton WW, Cascella NG, Fasano A, Kelly DL. Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity. *Psychiatr Q*. 2012 **83**: 91-102.
- [28]. Caruso R, Marafini I, Sedda S, *et al*. Analysis of the cytokine profile in the duodenal mucosa of refractory coeliac disease patients. *Clin Sci (Lond)*. 2014 **126**: 451-458.
- [29]. Russo F, Chimienti G, Linsalata M, Clemente C, Orlando A, Riezzo G. The obestatin/ghrelin ratio and ghrelin genetics in adult celiac patients before and after a gluten-free diet, in irritable bowel syndrome patients and healthy individuals. *Eur J Gastroenterol Hepatol*. 2017 **29**: 160-168.
- [30]. Oztas B, Sahin D, Kir H, *et al*. The effect of leptin, ghrelin, and neuropeptide-Y on serum Tnf-Alpha, Il-1beta, Il-6, Fgf-2, galanin levels and oxidative stress in an experimental generalized convulsive seizure model. *Neuropeptides*. 2017 **61**: 31-37.
- [31]. Portelli J, Michotte Y, Smolders I. Ghrelin: an emerging new anticonvulsant neuropeptide. *Epilepsia*. 2012 **53**: 585-595.
- [32]. Valletta E, Fornaro M, Cipolli M, Conte S, Bissolo F, Danchielli C. Celiac disease and obesity: need for nutritional follow-up after diagnosis. *Eur J Clin Nutr*. 2010 **64**: 1371-1372.

- [33]. Barone M, Della Valle N, Rosania R, *et al.* A comparison of the nutritional status between adult celiac patients on a long-term, strictly gluten-free diet and healthy subjects. *Eur J Clin Nutr.* 2016 **70**: 23-27.
- [34]. Mokdad AH, Ford ES, Bowman BA, *et al.* Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA.* 2003 **289**: 76-79.
- [35]. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet.* 2008 **371**: 569-578.
- [36]. Gao S, Juhaeri J, Dai WS. The incidence rate of seizures in relation to BMI in UK adults. *Obesity (Silver Spring).* 2008 **16**: 2126-2132.
- [37]. Lebwohl B, Murray JA, Rubio-Tapia A, Green PH, Ludvigsson JF. Predictors of persistent villous atrophy in coeliac disease: a population-based study. *Aliment Pharmacol Ther.* 2014 **39**: 488-495.
- [38]. Smedby KE, Akerman M, Hildebrand H, Glimelius B, Ekbom A, Askling J. Malignant lymphomas in coeliac disease: evidence of increased risks for lymphoma types other than enteropathy-type T cell lymphoma. *Gut.* 2005 **54**: 54-59.
- [39]. Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. *Lancet.* 2006 **367**: 1087-1100.

## TABLES

**Table 1:** Characteristics of patient cohort with CD and follow-up biopsies, excluding those patients who had a diagnosis of epilepsy prior to their follow-up biopsy (n=7,590)

Characteristic	Number (%)
Age at follow-up biopsy (years)	
Mean/Median/SD	30.5/26.8/24.8
0-19	3390 (45)
20-39	1318 (17)
40-59	1670 (22)
≥60	1212 (16)
Male	2790 (37)
Female	4800 (63)
Interval between diagnosis and follow-up biopsy	
6 months-1 year	2010 (26)
Between 1 and 2 years	3399 (45)
2-5 years	2181 (29)
Calendar period of follow-up biopsy	
≤1989	719 (9)
1990-1999	2877 (38)
≥2000	3994 (53)
Second biopsy result	
Mucosal healing	4295 (57)
Persistent villous atrophy	3295 (43)
Developed epilepsy	75 (1)

Mean/median/SD time between diagnosis of celiac disease and follow-up biopsy: 1.7/1.3/1.0 years

Mean/median/SD follow-up time (to epilepsy diagnosis, death, emigration, or December 31, 2009): 10.2/8.9/5.97 years

Of the 75 patients who developed a new diagnosis of epilepsy, the mean/median (SD) time from follow-up biopsy to epilepsy diagnosis was 7.1/6.2 (5.5) years.

**Table 2:** Association of persistent villous atrophy with epilepsy stratified by gender, age, and year of celiac disease diagnosis.

<b>Stratum</b>	<b>Number of events</b>	<b>Adjusted† HR (95% CI)</b>	<b>p value</b>
<b>Overall</b>			
Mucosal healing	45	1.0	
Persistent villous atrophy	30	0.61 (0.38-0.98)	0.04
<b>Gender</b>			
<b>Male</b>			
Mucosal healing	22	1.0	
Persistent villous atrophy	8	0.35 (0.15-0.80)	0.01
<b>Female</b>			
Mucosal healing	23	1.0	
Persistent villous atrophy	22	0.85 (0.46-1.57)	0.2620
<b>Age at follow-up biopsy</b>			
<b>&lt;20</b>			
Mucosal healing	25	1.0	
Persistent villous atrophy	14	0.61 (0.30-1.25)	0.1745
<b>20-39</b>			
Mucosal healing	4	1.0	
Persistent villous atrophy	2	0.77 (0.14-4.36)	0.7669
<b>40-59</b>			
Mucosal healing	8	1.0	
Persistent villous atrophy	7	0.61 (0.21-1.80)	0.7934
<b>≥60</b>			
Mucosal healing	8	1.0	
Persistent villous atrophy	7	0.66 (0.23-1.87)	0.4362
<b>Calendar Year</b>			
<b>1989 and before</b>			
Mucosal healing	6	1.0	
Persistent villous atrophy	5	0.29 (0.09-1.00)	0.0503
<b>1990-1999</b>			
Mucosal healing	21	1.0	
Persistent villous atrophy	19	0.66 (0.36-1.24)	0.1987
<b>2000 and after</b>			
Mucosal healing	18	1.0	
Persistent villous atrophy	6	0.75 (0.28-1.96)	0.5508

† Hazard Ratios (HR) are adjusted for patient age, gender, calendar period of diagnosis, education, and duration of celiac disease at the time of follow-up biopsy.