Published in final edited form as:

Eur J Neurol. 2014 July ; 21(7): 976–982. doi:10.1111/ene.12419.

No association between biopsy-verified celiac disease and subsequent amyotrophic lateral sclerosis – A population-based cohort study

Jonas F Ludvigsson, MD PhD^{a,b}, Daniela Mariosa, MS^a, Benjamin Lebwohl, MD, MS^{a,c}, and Fang Fang, MD PhD^a

^aDepartment Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, 17177 Sweden

^bDepartment of Pediatrics, Örebro University Hospital, Örebro University, Örebro, Sweden

^cCeliac Disease Center, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, USA

Abstract

Background and purpose—Earlier data suggest an association between amyotrophic lateral sclerosis (ALS) and autoimmune disease, but data on its association with celiac disease (CD) are limited.

Methods—We compared the risk of ALS in 29,093 individuals with CD according to small intestinal biopsy (villous atrophy, Marsh 3) carried out at Sweden's 28 pathology departments in 1969–2008, with that in 144,515 age- and sex-matched reference individuals from the general population. ALS was defined as a hospitalization or outpatient visit with ALS according to the Swedish Patient Register. Cox regression estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for ALS.

Results—During follow-up 12 (3.7/100 000 person-years) individuals with CD and 56 (3.5/100 000 person-years) reference individuals had a diagnosis of ALS. This corresponded to an HR of 1.0 (95% CI=0.5–1.8). HRs were significantly higher in the first year of follow-up (4.1; 1.2–13.4), than 1–5 years after first CD diagnosis (0.8; 0.2–2.7), or after more than 5 years of follow-up (0.5; 0.2–1.5). Relative risk estimates were similar in men and women, but were higher in the end of the study period (HR for ALS in patients diagnosed with CD in year 2000 or later was 2.1 (95% CI=0.9–4.8)).

Conclusion—This study found no association between CD and ALS. Earlier reports of a positive association may be due to surveillance bias just after CD diagnosis or expedited diagnostic work-up of ALS.

Corresponding author: Jonas F. Ludvigsson, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, 171 77 Stockholm, Sweden, Phone: +46 (0) 8-5248 2356, Fax: +46 (0) 8-31 49 75, jonasludvigsson@yahoo.com.

Conflict of Interest
None.

Key indexing terms

AUTOIMMUNE; COELIAC; GLUTEN; ALS; AMYOTROPHIC LATERAL SCLEROSIS

INTRODUCTION

Celiac disease (CD) is a chronic disorder characterized by small intestinal inflammation[1]. In sensitive individuals with characteristic HLA set up (DQ2+ and DQ8+)[2], it is triggered by exposure to gluten. Symptoms vary from classic malabsorption and growth failure to fatigue, osteoporosis and other extraintestinal symptoms[3]. The incidence of CD seems to have increased in recent decades[4, 5], and the prevalence now approaches 1–2% in the Western population[6, 7].

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease[8] where patients typically manifest with muscle atrophy, progressive weakness, fasciculations, and spasticity. Over time patients experience difficulties in swallowing, speaking, and breathing. Except for a minority of cases where there is a history of familial disease or evidence of a genetic component, the etiology of ALS is largely unknown [9]. Dietary factors and neurological traumas have both been suggested, as have exposure to chemicals [10, 11].

In the early 1990s Appel *et al*[12] and Kawamata *et al*[13] reviewed the evidence for autoimmunity in ALS. While an earlier case-control study failed to show an association with autoimmunity[14], British researchers recently reported a 15% overall excess risk of autoimmune disease in ALS, and specifically a 57% increased risk of prior CD (95%CI relative risk=1.13–2.12)[15]. We[16, 17], and others[18] have earlier reported an increased risk of certain neurological manifestations in CD, but data on ALS and CD have, with the exception of the British study,[15] been sparse[19].

We hypothesized that patients with CD are at increased risk of subsequent ALS. Linking nationwide histopathology data on CD with ALS data from the Swedish Patient Registry[20] we examined this hypothesis.

MATERIALS AND METHODS

Study participants

Data on duodenal and jejunal biopsies performed in 1969–2008 were obtained from biopsy records. Biopsy record data were collected between October 2006 and February 2008 from Sweden's 28 pathology departments (Table 1). We collected data on date of biopsy, site of the small intestinal biopsy (duodenum or jejunum), morphology codes consistent with villous atrophy (VA) (see appendix), and personal identity number (PIN)[21]. We then matched each individual with CD (definition below) with up to 5 reference individuals from the Total Population Register. Matching variables were age, sex, calendar year and county of residence at time of biopsy.[22] The original dataset consisted of 29,096 celiac patients and 144,522 controls (identical to that of our study on mortality in CD[23]).

Celiac Disease

We defined CD as having a biopsy report with VA (Marsh stage 3[24]). The CD diagnosis was not conditional on having a positive CD serology but in a subset of individuals undergoing patient chart validation and with available serology data, 88% had a positive serology against transglutaminase, endomysium or gliadin at time of biopsy. Detailed information on the data collection and validation of the CD diagnosis has been published elsewhere.[25] Biopsy report data on morphology were based on a mean of 3 tissue specimens.[26]

Amyotrophic lateral sclerosis

We defined ALS as having an inpatient or hospital-based outpatient diagnosis of ALS according to relevant international classification of disease (ICD) code in the Swedish Patient Register: ICD7: 356.10; ICD8: 348.00; ICD9: 335C; ICD10: G12.2. We included individuals with primary or secondary diagnoses of ALS.

We then excluded two individuals with ALS diagnosis before CD (n=1) or study entry (n=1 reference individual) respectively, and four individuals (CD: n=2, and reference individuals: n=2) due to data irregularities (potentially incorrect date of death). Finally we excluded another 4 reference individuals because their index individual with CD had been excluded and analyses were performed stratumwise (and any stratum without either a case with CD, or without any reference individuals, was automatically omitted from the analyses).

The final dataset therefore consisted of 29,093 individuals with CD and 144,515 reference individuals (Table 1).

Other covariates

We obtained data on the following potential confounding factors from the government agency *Statistics Sweden*: country of birth (Nordic vs. not Nordic), educational level, and socioeconomic status at time of biopsy. In children without data on socioeconomic status or education level we used parental data. We carried out a supplementary analysis (crude and adjusted) restricted to individuals with complete data on socioeconomic status or education (69.3% and 96.0% of individuals with CD). Education was divided into four groups (9 years of primary school, 2 years of high school, 3–4 years of high school, college/university) and socioeconomic status into six groups (according to the European Socioeconomic Classification, ESeC: levels 1, 2, 3+6, 7, 8, and 9). (For further details see Olén *et al*[27].)

Through the Patient Register we also identified data on type 1 diabetes and autoimmune thyroid disease (for definitions see appendix) since both CD and ALS have been linked to these diseases.

Statistics

We used Cox regression models to estimate hazard ratios (HRs) of developing ALS. The statistical model was internally stratified and thereby resembling a conditional logistic regression since all comparisons were made within the same stratum (defined by the matching variables). We tested the proportional hazards assumption through log-minus-log

curves (appendix), and found that the proportional hazards assumption was valid. Follow-up *began* on the date of 1st biopsy with VA (equivalent to CD in our study) and on the corresponding index date in the matched reference individuals, and *ended* when any of the following occurred: ALS diagnosis, December 31, 2009, emigration, or death.

In a priori defined analyses we examined the HR for ALS according to sex, age at CD diagnosis, and calendar period. We also examined potential effect modification of these variables, introducing interaction terms in the models. We also performed separate analyses adjusting for country of birth, level of education, socioeconomic status, type 1 diabetes, and autoimmune thyroid disease. We also introduced interaction terms to test for effect modification by sex, age and calendar period.

In a posthoc analysis we examined time from ALS diagnosis until death according to CD status, as well as reported cause of death.

We used SPSS 20 to calculate statistics. P-values <0.05 were considered statistically significant.

Ethics

This study was approved by the Regional Ethical Review Board in Stockholm (2006/633-31/4). Because this was a register-based study, no participant was contacted and all data were anonymised prior to data analyses.

RESULTS

Age at first biopsy with CD ranged between 0–95 years (median: 30 years). More than 85% of the study participants entered the study in the 1990s or later (Table 1; range 1969– 2008). The median age at first ALS diagnosis was 71 years in individuals with CD, and 67 years in reference individuals. The median duration from CD diagnosis to ALS diagnosis was 3 years and the duration between study entry and ALS diagnosis was 7 years in reference individuals (Figure 1). The majority of individuals were born in the Nordic countries (96.7% of CD vs. 94.3% of reference individuals).

Risk of future ALS

During a follow-up of 326,476 person-years, 12 celiac individuals had a diagnosis of ALS (3.7/100,000 person-years) during follow-up. This compares with 56 reference individuals with an ALS diagnosis during 1,601,276 person-years (3.5/100,000 person-years).

Restricting our dataset to individuals diagnosed with CD at 60 years or later (and corresponding date in controls), the ALS incidence was 16.0 and 12.3 per 100,000 person-years respectively).

The overall HR for ALS was 1.0 (95%CI=0.5–1.8)(Table 2), and did not change more than marginally with adjustment for socioeconomic status, education and country of birth (data not shown). Also when we used age as our time scale was the HR 1.0 (95%CI=0.5–1.8).

However in the first year after follow-up, we found a positive association between CD and ALS (Table 2).

Restricting our dataset to individuals with complete data on socioeconomic status and education did not influence our risk estimates (both crude and adjusted HRs=0.9).

When we excluded the first year of follow-up, the HR decreased somewhat (HR=0.6) but remained statistically non-significant (95%CI=0.3–1.4).

The HR for ALS was 0.8 in females (based on 4 celiac individuals with later ALS) and 1.1 in males (based on 8 celiac individuals)(p for multiplicative interaction between CD and sex: 0.375).

The HRs of ALS differed by calendar period (p for multiplicative interaction between CD and calendar period: 0.032), with low HRs in the first two calendar periods (0.6 and 0.4 respectively) and a HR above 2 after year 2000 (HR=2.14; 95%CI=0.9–4.8) (Table 3).

Death in ALS

When calculating HRs for ALS in patients with CD, we used data from the Inpatient Registry until Dec 31, 2009. However, data on date of death is updated more frequently and we therefore had data on date of death until Dec 31, 2010, but only data on cause of death until Dec 31, 2009.

Out of 12 CD patients with ALS, 9 (75%) died prior to Dec 31, 2010. The median time from ALS diagnosis until death was 207 days (range 3 to 454 days). Of 8 individuals with a reported cause of death, 7 (88%) died from ALS and 1 from heart disease. Out of 56 reference individuals with ALS, 49 died (88%). The median time from ALS diagnosis until death in these individuals was 295 days (range 1 to 3595 days). Of 37 individuals with reported cause of death, 31 (84%) died from ALS. Three patients died from cardiovascular disease, and the remaining three patients died from diabetes, disease in the autonomous nervous system and gastrointestinal disease.

DISCUSSION

This nationwide population-based study found no association between CD and future ALS. However, we saw a highly increased risk in the first year after CD diagnosis, while decreased risk in the following years, suggesting surveillance bias just after diagnosis. In their recent paper on autoimmune disease and ALS, Turner *et al* found an increased risk of ALS in patients with prior CD (relative risk=1.57; 95%CI=1.13–2.12)[15].

There may be several reasons why we found a neutral association between CD and ALS while Turner *et al* reported a positive association. We ascertained CD through pathology registers while Turner *et al* identified individuals with CD through British Hospital data. Ascertainment of diagnoses that not always require hospital admission through hospital-based registers will often overestimate relative risks of comorbidity. For instance, hospital-based CD is associated with a 3.7-fold increased risk of tuberculosis[28], while the relative risk for tuberculosis is only 2.0 for CD identified through pathology-registers[29].

Length of follow-up is another factor that may influence risk estimates for ALS in CD. In our study, the median duration between CD diagnosis and ALS was 3 years compared to 7 years in reference individuals (our mean follow-up was 11 years)(Figure 1). We speculate that shorter time to ALS diagnosis in celiac patients is due to surveillance bias and expedited work up for ALS in celiac patients. In studies with shorter follow-up, the high relative risks immediately after diagnosis will have a high impact on the overall relative risk.

Turner *et al* do not present data on mean follow-up [15] in their paper but refer to e.g. Seminog *et al* [30] for methodological details. In that paper[30], the mean follow-up in the all-England linked Hospital Episode Statistics dataset was 6 years [15] (compared to 11 years in our study). When in a post-hoc analysis we restricted our follow-up to the first six years, the HR for ALS in Swedish individuals with CD rose to 1.49 (95%CI=0.68–3.29), i.e. very similar to the 1.57 reported in the British study. In our study, a high ALS diagnostic rate just after CD diagnosis was then followed by a lower than expected diagnostic rate thereafter with an overall neutral relative risk of ALS in CD (HR=1.0), as can be seen from Figure 1. Shorter follow-up may also explain the higher HRs for ALS in patients diagnosed with CD 2000–08 since these patients had shorter follow-up than CD individuals diagnosed in the 1980s and 1990s.

Finally, despite differences in diagnostic ascertainment and length of follow-up, it is still possible that our study and that of Turner *et al* are consistent since 95%CIs overlapped (Sweden: 0.5–1.8 vs. Britain: 1.13–2.12 [15]).

Our study has some strengths and some limitations. Besides the nationwide inclusion of individuals with CD and ALS, the long follow-up and the large number of patients is the main strength of our paper. That said, we cannot rule out a minor risk increase for ALS and CD since our upper 95%CI was 1.8. We used histopathology data from Sweden's all pathology departments to ascertain individuals with CD. In our study we equated histopathology Marsh stage 3 (villous atrophy [24]) with CD. An earlier chart validation by our research group of 114 randomly selected patients showed that 95% of patients with VA in Sweden have CD[25] (that is a higher positive predictive value than using physician-assigned diagnostic codes in the Swedish Patient Registry [31]). And when we (2 independent researchers) reviewed > 1500 biopsy reports with either villous atrophy or inflammation,[25] we found that other diagnoses than CD were uncommon (in 0.3% of the biopsy-reports with villous atrophy represented IBD). Finally, biopsy reports have a high sensitivity for CD since 96–100% of all Swedish gastroenterologists and pediatricians biopsied their patients before CD diagnosis at the time of our data collection.[25] We lacked information on dietary compliance in CD, though this is probably less of a shortcoming since our study did not find a positive association with ALS and poor compliance is unlikely to explain our results. The current study concerned the risk of ALS among patients with diagnosed CD, and many patients with CD remain undiagnosed[32]; the risk of ALS in undiagnosed (and thus untreated) CD cannot be inferred from this study.

Although the ALS diagnosis has not yet been validated in the Swedish Patient Registry, most diagnoses in this registry have a positive predictive value of 85–95%.[20] However the lack of clinical data on disease onset and genetic data in patients with ALS is a limitation.

The association between CD and ALS might be specifically applicable to certain subgroups of ALS patients. Furthermore, careful assessment of ALS is important as the disease may mimic gluten ataxia seen in CD[19, 33]. Brown *et al* reported a 32-year-old man with a history of balance difficulties and gait disturbance where initial diagnostic considerations included ALS and Friedrich ataxia. Ataxia work-up revealed positive anti-endomysial antibodies and the patient was started on a gluten-free diet after which symptoms improved and the brain MR findings disappeared[19]. Also, Turner *et al* have noted the similarities between ALS and CD in a case-report of a 44-years-old man with hemiparesis and wasting who responded to a gluten-free diet[33]. The observations above would however have been more relevant if we had found a strong positive association between the two diseases.

Unfortunately this paper lacked information on a number of potential confounders. In a recent paper, O'Reilly *et al* showed that underweight men were at a 2.5-fold increased risk of ALS[34]. This is interesting since a similar association has been seen for men with hospital-based CD (odds ratio =2.4)[35]. Hence, weight may be an important confounder, though such a confounder would bias the result away from the null, and our negative finding suggests that this lack of data does not substantially contribute to bias. It is possible that the positive association in the Turner *et al* paper[15] was driven by shared underweight. In contrast the current study did not rely on hospital admission to identify CD and our patients are therefore probably less likely to suffer from underweight than in a hospital setting.

Conclusion

Although we cannot rule out a minor excess risk of ALS in patients with CD, our risk estimates were consistently null except for in the first year after CD diagnosis. Earlier reports of a positive association between CD and ALS may be due to insufficient follow-up, and surveillance bias in individuals with newly diagnosed CD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

JFL was supported by grants from the Swedish Society of Medicine, the Swedish Research Council, and the Swedish Celiac Society,.

BL was supported by The National Center for Advancing Translational Sciences, National Institutes of Health (UL1 TR000040)

FF was supported by grants from the Swedish Research Council, Svenska Sällskapet för Medicinsk Forskning (SSMF), and the Karolinska Institutet.

None of the funders had any influence on this study.

Abbreviations used in this article:

ALS amyotrophic lateral sclerosis

CD	Celiac disease
CI	Confidence Interval
HR	Hazard ratio
ICD	International Classification of Disease (codes)
OR	Odds ratio
VA	Villous atrophy

REFERENCES

1. Ludvigsson JF, Green PH. Clinical management of coeliac disease. *J Intern Med*. 2011; 269:560–571. [PubMed: 21443532]
2. Sollid LM. Molecular basis of celiac disease. *Annu Rev Immunol*. 2000; 18:53–81. [PubMed: 10837052]
3. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. *Gut*. 2013; 62:43–52. [PubMed: 22345659]
4. Lohi S, Mustalahti K, Kaukinen K, et al. Increasing prevalence of coeliac disease over time. *Aliment Pharmacol Ther*. 2007; 26:1217–1225. [PubMed: 17944736]
5. Ludvigsson JF, Rubio-Tapia A, van Dyke CT, et al. Increasing incidence of celiac disease in a north american population. *Am J Gastroenterol*. 2013; 108:818–824. [PubMed: 23511460]
6. Dube C, Rostom A, Sy R, et al. The prevalence of celiac disease in average-risk and at-risk Western European populations: a systematic review. *Gastroenterology*. 2005; 128:S57–S67. [PubMed: 15825128]
7. Walker MM, Murray JA, Ronkainen J, et al. Detection of Celiac Disease and Lymphocytic Enteropathy by Parallel Serology and Histopathology in a Population- Based Study. *Gastroenterology*. 2010; 139:112–119. [PubMed: 20398668]
8. Phukan J, Pender NP, Hardiman O. Cognitive impairment in amyotrophic lateral sclerosis. *Lancet Neurol*. 2007; 6:994–1003. [PubMed: 17945153]
9. Renton AE, Chio A, Traynor BJ. State of play in amyotrophic lateral sclerosis genetics. *Nat Neurosci*. 2014; 17:17–23. [PubMed: 24369373]
10. Al-Chalabi A, Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment and time. *Nat Rev Neurol*. 2013; 9:617–628. [PubMed: 24126629]
11. Trojsi F, Monsurro MR, Tedeschi G. Exposure to environmental toxicants and pathogenesis of amyotrophic lateral sclerosis: state of the art and research perspectives. *Int J Mol Sci*. 2013; 14:15286–15311. [PubMed: 23887652]
12. Appel SH, Smith RG, Engelhardt JI, Stefani E. Evidence for autoimmunity in amyotrophic lateral sclerosis. *J Neurol Sci*. 1993; 118:169–174. [PubMed: 8229065]
13. Kawamata T, Akiyama H, Yamada T, McGeer PL. Immunologic reactions in amyotrophic lateral sclerosis brain and spinal cord tissue. *Am J Pathol*. 1992; 140:691–707. [PubMed: 1347673]
14. Armon C, Kurland LT, O'Brien PC, Mulder DW. Antecedent medical diseases in patients with amyotrophic lateral sclerosis. A population-based case-controlled study in Rochester, Minn, 1925 through 1987. *Arch Neurol*. 1991; 48:283–286. [PubMed: 2001186]
15. Turner MR, Goldacre R, Ramagopalan S, Talbot K, Goldacre MJ. Autoimmune disease preceding amyotrophic lateral sclerosis: An epidemiologic study. *Neurology*. 2013
16. 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. [PubMed: 17509100]
17. 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. [PubMed: 22517096]

18. Hadjivassiliou M, Sanders DS, Woodroffe N, Williamson C, Grunewald RA. Gluten ataxia. *Cerebellum*. 2008; 7:494–498. [PubMed: 18787912]
19. Brown KJ, Jewells V, Herfarth H, Castillo M. White matter lesions suggestive of amyotrophic lateral sclerosis attributed to celiac disease. *AJNR Am J Neuroradiol*. 2010; 31:880–881. [PubMed: 19910450]
20. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011; 11:450. [PubMed: 21658213]
21. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009; 24:659–667. [PubMed: 19504049]
22. Johannesson, I. The Total Population Register of Statistics Sweden. New Possibilities and Better Quality. Statistics Sweden: Örebro; 2002.
23. Ludvigsson JF, Montgomery SM, Ekbom A, Brandt L, Granath F. Smallintestinal histopathology and mortality risk in celiac disease. *Jama*. 2009; 302:1171–1178. [PubMed: 19755695]
24. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). *Gastroenterology*. 1992; 102:330–354. [PubMed: 1727768]
25. 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. [PubMed: 19284576]
26. Ludvigsson JF, Brandt L, Montgomery SM. Symptoms and signs in individuals with serology positive for celiac disease but normal mucosa. *BMC Gastroenterol*. 2009; 9:57. [PubMed: 19624815]
27. Olen O, Bihagen E, Rasmussen F, Ludvigsson JF. Socioeconomic position and education in patients with coeliac disease. *Dig Liver Dis*. 2012
28. Ludvigsson JF, Wahlstrom J, Grunewald J, Ekbom A, Montgomery SM. Coeliac disease and risk of tuberculosis: a population based cohort study. *Thorax*. 2007; 62:23–28. [PubMed: 17047199]
29. Ludvigsson JF, Sanders DS, Maeurer M, Jonsson J, Grunewald J, Wahlstrom J. Risk of tuberculosis in a large sample of patients with coeliac disease--a nationwide cohort study. *Aliment Pharmacol Ther*. 2011; 33:689–696. [PubMed: 21251029]
30. Seminog OO, Goldacre MJ. Risk of pneumonia and pneumococcal disease in people with severe mental illness: English record linkage studies. *Thorax*. 2013; 68:171–176. [PubMed: 23242947]
31. 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. [PubMed: 15591504]
32. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. *Am J Gastroenterol*. 2012; 107:1538–1544. quiz 1537, 1545. [PubMed: 22850429]
33. Turner MR, Chohan G, Quaghebeur G, Greenhall RC, Hadjivassiliou M, Talbot K. A case of celiac disease mimicking amyotrophic lateral sclerosis. *Nat Clin Pract Neurol*. 2007; 3:581–584. [PubMed: 17914346]
34. O'Reilly EJ, Wang H, Weisskopf MG, et al. Premorbid body mass index and risk of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2013; 14:205–211. [PubMed: 23134505]
35. Olen O, Montgomery SM, Marcus C, Ekbom A, Ludvigsson JF. Coeliac disease and body mass index: A study of two Swedish general population-based registers. *Scand J Gastroenterol*. 2009; 44:1198–1206. [PubMed: 19672788]

APPENDIX: ICD (international classification of disease) codes

Table 1a. Comparison of small intestinal histopathology classifications

<i>Classification used in this project</i>	<i>Villous atrophy</i>		
Marsh Classification	Type IIIa	Type IIIb	Type IIIc
Marsh Description	Flat destructive		
Corazza <i>et al</i> (A)	Grade B1		Grade B2
SnoMed Codes	M58, D6218, M58005	M58, D6218, M58006	M58, D6218, M58007
KVAST/Alexander classification	III Partial VA	IV Subtotal VA	IV Total VA
<i>Characteristics</i>			
Villous atrophy	+	++	++
IEL#	+	+	+
Crypt hyperplasia	+	++	++

Comparison of small intestinal histopathology classifications. REF A. Corazza GR, Villanacci V, Zambelli C, *et al.* Comparison of the interobserver reproducibility with different histologic criteria used in CD. *Clin Gastroenterol Hepatol.* Jul 2007;5(7):838-843.

Type 1 diabetes mellitus: Before 1997, the ICD coding for diabetes (ICD-7: 260, ICD-8: 250, ICD-9: 250) did not distinguish between type 1 and type 2 diabetes. We defined individuals with type 1 diabetes as those who were ≥ 30 years of age at their first hospitalization for diabetes (ICD-7-ICD-10). ICD-10: E10.

Autoimmune thyroid disease: Autoimmune thyroid disease was defined as follows: ICD-7: 252.00, 252.01, 252.02, 253.10, 253.19, 253.20, 253.29, 254.00, ICD-8: 242.00, 242.09, 244, 245.03, ICD-9: 242A, 242X, 244X, 245C, 245W, ICD-10: E03.5, E03.9, E05.0, E05.5, E05.9, E06.3, E06.5.

Figure 1. Duration from celiac diagnosis and study entry (in reference individuals) until first diagnosis with ALS

1= Celiac disease

0= Reference individuals

TABLE 1

Characteristics of the study participants.

	<i>Matched controls</i>	<i>Celiac disease</i>
<i>Total</i>	144,515	29,093
Age at study entry, years (median, range)	30; 0–95	30; 0–95
Age 0–19 (%)	58,852 (40.7)	11,802 (40.6)
Age 20–39 (%)	26,383 (18.3)	5,312 (18.3)
Age 40–59 (%)	32,252 (22.3)	6,475 (22.3)
Age 60 (%)	27,028 (18.7)	5,504 (18.9)
Entry year (median, range)	1998, 1969–2008	1998, 1969–2008
Follow-up [#] , years (median, range)	10; 0–41	10; 0–41
Follow-up [#] , years (mean±SD)	11.4±6.5	11.2±6.5
Females (%)	89,543 (62.0)	18,004 (61.9)
Males (%)	54,972 (38.0)	11,089 (38.1)
<i>Calendar year</i>		
–1989	20,377 (14.1)	4,105 (14.1)
1990–99	59,871 (41.4)	12,059 (41.4)
2000–	64,267 (44.5)	12,929 (44.4)
Type 1 diabetes	596 (0.4)	956 (3.3)
Autoimmune thyroid disease	2,504 (1.7)	1,437 (4.9)

* Ages were rounded to the nearest year.

[#] Follow-up time until diagnosis of ALS, death, emigration or December 31, 2009. In reference individuals follow-up also ended with small intestinal biopsy.

TABLE 2

Relative risk of ALS based on follow-up time in individuals with celiac disease.

Follow-up	Events, CD	Events, Reference	HR; 95% CI
All	12	56	1.0; 0.5–1.8
Year <1	5	6	4.1; 1.2–13.4
1–4.99	3	18	0.8; 0.2–2.7
5	4	32	0.5; 0.2–1.5

HR, Hazard ratio; CI, Confidence interval.

Reference is general population comparator cohort

TABLE 3

Relative risk of ALS in relation to characteristics of patients with celiac disease.

Subgroup	Events, CD	Events, Reference	HR; 95% CI
<i>Sex</i>			
Males	8	31	1.1; 0.5–2.5
Females	4	25	0.8; 0.3–2.2
<i>Age</i>			
<20 yrs [#]	-	-	-
20–39 yrs	2	2	5.7; 0.7–42.8
40–59 yrs	3	28	0.6; 0.2–1.8
60+ yrs	7	26	1.1; 0.5–2.6
<i>Calendar period</i>			
-1989	1	9	0.6; 0.2–5.1
1990–1999	3	28	0.4; 0.1–1.4
2000–2008	8	19	2.1; 0.9–4.8

HR, Hazard ratio; CI, Confidence interval.

Reference is general population comparator cohort

[#] No individual with CD diagnosed before age 20 years developed ALS before end of follow-up.