

Risk of Dementia in Patients with Celiac Disease: A Population-Based Cohort Study

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Abstract.

Background: Patients with celiac disease (CD) frequently report cognitive symptoms when they are exposed to gluten, and cognitive deficits have been quantified in patients with newly diagnosed CD.

Objective: To determine whether patients with CD have an increased risk of dementia.

Methods: Using a population-based database of older adults (age ≥ 50 years) with histologically proven CD (duodenal/jejunal villous atrophy) from all 28 pathology departments in Sweden, we compared the incidence of a subsequent dementia diagnosis to those of age- and gender-matched controls.

Results: Among patients with CD ($n = 8,846$) and controls ($n = 43,474$), the median age was 63 years and 56% were female. During a median follow-up time of 8.4 years, dementia was diagnosed in 4.3% of CD patients and 4.4% of controls (HR 1.07; 95% CI 0.95–1.20). Although there was an increased risk of dementia in the first year following a diagnosis of CD (HR 1.73; 95% CI 1.15–2.61), this risk was not present in the whole observation period. Among those subjects with a dementia subtype specified, the increased risk was restricted to vascular dementia (HR 1.28; 95% CI 1.00–1.64) and was not present for Alzheimer's dementia (HR 1.12; 95% CI 0.91–1.37).

Conclusions: Patients with CD are not at increased risk for dementia overall, though subgroup analysis suggests that they may be at increased risk for vascular dementia.

Keywords: Alzheimer's disease, celiac disease, dementia, epidemiology

INTRODUCTION

Celiac disease (CD) is an immune-based enteropathy triggered by the ingestion of gluten, with a diverse array of intestinal and extra-intestinal symptoms [1]. Transient cognitive symptoms, colloquially referred to as “brain fog” by patients, are frequently reported after

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gluten ingestion, though a precise quantification and organic basis for this phenomenon is lacking [2, 3].

Recently, the gluten-free diet has been promoted to the general public for putative health benefits, including the reduction in risk of dementia [4, 5]. The rationale for this benefit is derived in part from the cognitive effects reported in patients with CD [4]. However, it is unknown whether patients with CD have an increased risk of dementia.

Neurologic manifestations of CD include peripheral neuropathy [6], migraine [7], and cerebellar ataxia [8], though in a proportion of patients these outcomes are mediated by vitamin deficiencies or another autoimmune disorder. In one recent retrospective study of 44 patients with CD and/or positive CD serologies and concomitant neurologic disease, dementia was present in 8 patients, ranking third after cerebellar ataxia and neuropathy [9].

Several case series have suggested a possible causal or exacerbating effect of gluten on patients with CD and dementia. Cognitive symptoms have been reported to improve after diagnosis of CD and institution of the gluten-free diet among patients with dementia [10–12]. To our knowledge, the only formal test of association between dementia and CD was a study in 1997 in which CD antibodies were measured in 33 patients with Alzheimer's dementia and 23 controls; [13] no patients with CD were identified in either group, but that null finding could be due to lack of power, given that CD is prevalent in approximately 0.8–1% of most Western populations [14, 15].

Two recent studies have shown a link between CD and cognitive impairment. Lichtwark and colleagues administered neuropsychiatric tests to 11 CD patients upon initial diagnosis and again three months and one year after starting a gluten-free diet [2]. They found deficiencies in tests of verbal fluency, attention, and motor function on initial diagnosis, and these deficiencies improved after intestinal recovery. In a study of elderly patients with longstanding CD, Casella, et al. compared 18 patients to age- and sex-matched controls, and found significant reductions in cognitive scores in the CD group, despite adhering to the gluten-free diet for a mean of 5.5 years [16]. It is difficult to reach a definitive conclusion regarding the cognitive effects of CD based on these small case series and studies; it appears that some cognitive symptoms are dynamic and responsive to gluten withdrawal while others may persist.

We aimed to quantify the risk of dementia in patients with histologically diagnosed CD in a nationwide population-based cohort of patients in Sweden with CD as compared to matched controls.

METHODS

Patients and controls

The derivation of patients with CD and controls has been described in detail previously [17–19]. Patients with CD were identified via Systematized Nomenclature of Medicine (SnoMed) codes corresponding to villous atrophy among small intestinal biopsy specimens submitted to all 28 Swedish pathology departments during the time period spanning July 1969 through February 2008. We restricted the eligible population to individuals age 50 years and older at the time of CD diagnosis who did not have a preexisting diagnosis of dementia.

At the time of CD case identification, each CD patient was matched by the government agency Statistics Sweden to up to 5 controls who did not have CD at the date of case diagnosis. Controls were matched by age (to the year), gender, calendar period (1989 and earlier, 1990–1999, and 2000 and after), and region within Sweden.

Dementia outcomes

We identified dementia outcomes based on inpatient or outpatient visits that included relevant international classification of disease (ICD) codes for dementia (see Supplementary Table 1). Swedish national registers have been used repeatedly to ascertain dementia [20, 21]. In a pre-planned analysis, we examined the risk of dementia subtypes in CD. Where the dementia subtype was available, we classified patients as having Alzheimer's dementia or vascular dementia; the remaining patients were categorized as having unclassified dementia.

Statistical analysis

We used a stratified Cox proportional hazards model to compare patients with CD to matched controls with regards to their risk of dementia. Observation time began on the date of CD diagnosis (i.e., date of small intestinal biopsy) or the corresponding date of inclusion as a control. Patients were followed until death (as derived from the Swedish Total Population Register), emigration, diagnosis of dementia, or December 31, 2009. As was the case in our previous investigation of mortality in CD, we adjusted for educational attainment [17].

The primary outcome was a diagnosis of dementia, as defined as the use of at least one dementia diagnosis

code for any inpatient or outpatient visit. We calculated an overall Hazard Ratio, and conducted a stratified analysis according to the time elapsed since the diagnosis of CD: less than 1 year, 1–4.99 years, and ≥ 5 years. We performed this time-dependent stratified analysis due to the phenomenon of dynamic risk of morbidity after CD diagnosis that has been reported previously, with risks diminishing over time [17, 22]. We investigated effect modification by testing the interaction term between CD and the following variables: age, gender, and calendar period of study entry. We then repeated the Cox proportional hazard models in which the outcome was one of three dementia subtypes: Alzheimer's dementia, vascular dementia, and unclassified dementia.

Because the diagnosis of CD can be delayed for years [23], we also investigated the association between CD and a previous diagnosis of dementia. For that analysis, we performed conditional logistic regression, comparing CD patients to matched controls (again adjusting for educational attainment), with regard to any previous diagnosis of dementia.

Sensitivity analyses

To test the robustness of our findings, we performed the following three sensitivity analyses:

- 1) Because of the possibility of ascertainment bias (i.e., patients newly diagnosed with CD may be more likely to be extensively evaluated and found to have dementia), we excluded patients whose dementia was diagnosed in the first 6 months following CD diagnosis (or corresponding date of inclusion as a control).
- 2) We restricted the definition of dementia to those with at least 2 visits associated with a diagnosis of dementia.
- 3) We restricted our analysis to those patients who were diagnosed in the most recent time stratum, i.e., 2000 and onward.

All statistical calculations were performed using SAS version 9.4 (Cary, North Carolina). We report Hazard Ratios with their corresponding 95% confidence intervals. All reported *p* values are 2-sided. This project (2006/633-31/4) was approved by the Research Ethics Committee of the Karolinska Institute, Sweden on June 14, 2006.

RESULTS

Among CD patients aged ≥ 50 years ($n = 8,872$) and matched controls ($n = 43,811$), we excluded 26 CD

Table 1
Characteristics of patients age ≥ 50 years with celiac disease and matched controls

Characteristic	CD ($n = 8,846$)	Controls ($n = 43,474$)
Age at study entry (years)		
Mean/Median/SD	64/63/9.7	64/63/9.6
50–59	3,366 (38)	16,768 (39)
60–69	2,806 (32)	13,888 (32)
≥ 70	2,674 (30)	12,818 (29)
Gender		
Male	3,910 (44)	19,146 (44)
Female	4,936 (56)	24,328 (56)
Calendar period of study entry		
≤ 1989	1,019 (12)	5,003 (12)
1990–1999	3,740 (42)	18,359 (42)
≥ 2000	4,087 (46)	20,112 (46)
Developed dementia	376 (4.3)	1,902 (4.4)

Table 2
Association of CD with subsequent diagnosis of dementia stratified by follow-up time. Test for heterogeneity between time strata: $p = 0.0490$

Stratum	Number of events	Adjusted* HR (95% CI)	<i>p</i> value
Overall			
Controls	1,902	1.0	
Celiac disease	376	1.07 (0.95–1.20)	0.2940
<1 year			
Controls	95	1.0	
Celiac disease	31	1.73 (1.15–2.61)	0.0092
1–5 years			
Controls	520	1.0	
Celiac disease	100	0.97 (0.78–1.21)	0.7782
>5 years			
Controls	1287	1.0	
Celiac disease	245	1.05 (0.91–1.22)	0.4966

*Adjusted for education level.

patients and 337 controls due to a preexisting dementia diagnosis at the time of inclusion. Among the remaining 8,846 CD patients and 43,474 controls (Table 1), the median age was 63 years and 56% were female. Nearly half of CD patients and controls began their follow-up time after the year 2000. The median follow-up time was 8.1 years for CD patients and 8.5 years for controls. During this period, 376 CD patients (4.3%) and 1,902 (4.4%) controls developed dementia. The overall incidence of dementia in CD patients and controls was 462 per 100,000 person-years of observation; among individuals 65 years and older, the incidence was 965 per 100,000 person-years of observation.

On Cox proportional hazards, there was no overall significant increase in dementia among CD patients compared with controls (HR 1.07; 95% CI 0.95–1.20, $p = 0.29$) during 492,793 person-years of follow-up.

Table 3
Association of CD with dementia stratified by age

Stratum	Number of events	Adjusted* HR (95% CI)	p value
Overall			
Controls	1,902	1.0	
Celiac disease	376	1.07 (0.95–1.20)	0.2940
Age at Study Entry			
50–59			
Controls	205	1.0	
Celiac disease	49	1.31 (0.95–1.81)	0.1031
60–69			
Controls	520	1.0	
Celiac disease	116	1.34 (1.08–1.66)	0.0077
≥70			
Controls	1,177	1.0	
Celiac disease	211	0.91 (0.78–1.07)	0.2710
			[p for interaction = 0.0132]

*Adjusted for education level.

Table 4
Association of CD with dementia subtype

Stratum	Number of events	Adjusted* HR (95% CI)	p value
<i>Alzheimer's dementia</i>			
Controls	593	1.0	
Celiac disease	125	1.12 (0.91–1.37)	0.2905
<i>Vascular dementia</i>			
Controls	380	1.0	
Celiac disease	90	1.28 (1.00–1.64)	0.0491
<i>Non-classified dementia</i>			
Controls	929	1.0	
Celiac disease	161	0.94 (0.78–1.13)	0.4906

*Adjusted for education level.

Removing educational attainment from the Cox model had no effect (HR 1.07; 95% CI 0.95–1.20, $p = 0.29$). On time-stratified analysis (Table 2), there was a modest and statistically significant increase in dementia risk in the first year following CD diagnosis (HR 1.73; 95% CI 1.15–2.61, $p = 0.009$), but with no increase noted in the intermediate-and-long term.

When testing for interaction, we found evidence of effect modification between CD and age ($p = 0.01$, Table 3). There was a significant association between CD and dementia among the age group 60–69 (HR 1.34; 95% CI 1.08–1.66, $p = 0.008$) that was not present in the younger or older age strata, though the point estimate for the younger age stratum was similar (HR 1.31; 95% CI 0.95–1.81, $p = 0.10$). There was no evidence of interaction between CD and gender ($p = 0.14$) or calendar period of diagnosis ($p = 0.99$) with regard to the association with dementia.

When investigating dementia subtypes (Table 4), we found that of 2,278 patients with dementia, 718 (32%) were diagnosed with Alzheimer's dementia, 470

(21%) were diagnosed with vascular dementia, and the remaining 1,090 (48%) had unclassified dementia. Those with unclassified dementia had a greater female predominance (60%) compared to those with classified dementia (54%, $p = 0.005$). Those with unclassified dementia also had a greater mean age of dementia diagnosis compared to those with classified dementia (82.2 versus 78.4 years, $p < 0.0001$). There appeared to be an increased risk of vascular dementia among patients with CD (HR 1.28; 95% CI 1.00–1.64, $p = 0.05$) but no increased risk of Alzheimer's dementia (HR 1.12; 95% CI 0.91–1.37, $p = 0.29$). The increased risk of vascular dementia in CD patients was highest in the first year after CD diagnosis (HR 2.73; 95% CI 1.15–6.48, $p = 0.02$), and was of borderline significance 5 years after CD diagnosis (HR 1.32; 95% CI 0.97–1.81, $p = 0.08$).

Celiac disease and prior diagnosis of dementia

In contrast to the modest increased risk of dementia seen after diagnosis of CD, we found that a dementia diagnosis was less likely to be made prior to a diagnosis of CD compared to controls. Among 8,872 patients with CD, 26 (0.3%) were previously diagnosed with dementia; among 43,811 controls, 337 (0.8%) were previously diagnosed with dementia. This inverse relationship was significant on conditional logistic regression, adjusting for educational attainment (OR 0.36; 95% CI 0.24–0.54, $p < 0.0001$).

Sensitivity analyses

When we excluded patients whose dementia was diagnosed in the first 6 months following CD diagnosis (or corresponding date of inclusion as a control), this resulted in the exclusion of 18 cases of dementia among patients with CD and 47 cases of dementia among controls. This had a negligible effect on the estimate made in our primary analysis (HR 1.04; 95% CI 0.92–1.17, $p = 0.55$). The estimate was also similar when we restricted the definition of dementia to those with at least 2 visits associated with a diagnosis of dementia (HR 1.12; 95% CI 0.95–1.33, $p = 0.16$). Finally, when we restricted the analysis to those patients diagnosed with CD in the year 2000 and onwards, our results were similarly null (HR 1.06; 95% CI 0.85–1.32, $p = 0.62$).

DISCUSSION

In this population-based cohort study of patients with histologically confirmed CD, we found no overall

increased hazard ratio for a subsequent diagnosis of dementia compared to controls. There was a detectable increase that was limited to the first year after CD diagnosis (HR 1.73; 95% CI 1.15–2.61, $p=0.03$), suggestive of ascertainment bias. Subgroup analysis found that CD appeared to be associated with vascular dementia (HR 1.28; 95% CI 1.00–1.64, $p=0.05$) but not Alzheimer's dementia (HR 1.12; 95% CI 0.91–1.37, $p=0.29$). Though a larger sample size might detect a smaller effect, we can state with 95% confidence that the overall risk of dementia in CD patients compared to controls does not exceed 1.20.

The relationship between cognitive function and gluten in general and CD in particular is a topic of popular interest [4, 5], but there is a paucity of rigorous studies in this area. Proposed mechanisms by which gluten could mediate cognitive impairment include vitamin deficiencies [9], circulating cytokines associated with inflammation [24], antibody-mediated effects [9], direct neurohormonal effects of gluten peptides [25], and effects of the diet on the microbiome [26]. This is the first study that tests for an association between CD and a subsequent diagnosis of dementia. It is reassuring that we did not find a strong increased risk, and it is possible that the modest increased risk of dementia seen in the first year after diagnosis of CD is due to ascertainment bias, as patients with newly diagnosed CD may be more likely to be diagnosed with additional indolent conditions that previously eluded medical attention. This transient increased risk is analogous to the rise in gastrointestinal cancers seen in the same cohort in the first year after CD diagnosis [27].

While the increased risk of vascular dementia may also be subject to ascertainment bias (as the HR for the first year after the CD diagnosis was 2.73), the persistently elevated risk of this dementia subtype is concerning given the known association between CD and a small increased risk of both cardiovascular [28] and cerebrovascular disease [29]. While the mechanism by which CD could increase the risk of vascular dementia is unknown, the increased risk is consistent with prior findings of cardiovascular and cerebrovascular disease. It is known that CD is associated with deficiency of homocysteine related vitamins such as B12, and homocysteine is a putative risk factor for cerebrovascular disease [30] and dementia [31]. Thus, it is possible that higher homocysteine levels in persons with CD could be related to vascular dementia. A link to vascular dementia is also consistent with reports of white matter lesions on neuroimaging of CD patients (both adults [32] and children [33]) with neurologic symptoms. In one series of 10 patients with

elevated antigliadin antibodies and ataxia (4 of whom had biopsy evidence of CD), MRI showed white matter abnormalities characterized by multiple T2 signal hyperintensities in a vascular pattern [34]. We did not have access to data regarding risk factors for vascular disease or cardiovascular disease-related medications in this analysis. Overall this *post-hoc* finding of an increased risk of vascular dementia should be seen as hypothesis-generating and may encourage further study for confirmation and elucidation of mechanisms.

Strengths of this study include its sample size, including 376 CD patients who subsequently developed dementia, and its follow-up time of nearly a decade. The population-based setting is an additional strength, diminishing the likelihood of selection bias. Our study also has a number of limitations. We relied on diagnosis codes in our ascertainment of dementia outcomes, leading to the possibility of misclassification. An earlier validation has shown a high specificity for dementia diagnoses in Swedish healthcare [21]. Although we cannot rule out that specificity is slightly lower in outpatient care, we performed a series of sensitivity analyses using more stringent definitions of dementia, and our results were largely unchanged. We did not have information on which patients had a low body mass index, a possible mediator of any association between CD and the development of dementia [35]. It is possible that some patients diagnosed with CD did not undergo an initial diagnostic biopsy, and such patients may be qualitatively different from patients in this database; however, a prior validation study revealed that more than 95% of gastroenterologists and pediatricians in Sweden report routinely perform a biopsy to diagnose CD [19].

Our CD population consists of those patients who were ultimately diagnosed with CD, unlike the majority of CD patients who remain undiagnosed [36]. Examining diagnoses of dementia prior to CD diagnosis is one approach to investigating undiagnosed CD, but patients after receiving a diagnosis of dementia were far less likely to undergo the necessary invasive procedure (small intestinal biopsy) for CD diagnosis. This is the most plausible explanation for our finding of a strong inverse relationship between dementia diagnosis and subsequent CD diagnosis. Therefore, the impact of undiagnosed (and untreated) CD on dementia risk remains uncertain. The outcome of dementia is likewise also under-diagnosed; this study relied on claims codes and patients with dementia may not have been formally tested and diagnosed. Assuming that misclassification is not differential by CD status, such misclassification may bias the findings towards the null, as subtle cognitive

differences between the two groups may have been missed. Given that both CD and dementia can be diagnosed long after symptoms first develop, the temporal order of disease onset cannot be known with certainty. Although there is increasing interest in the effects of gluten consumption on health outcomes (cognitive or otherwise) in the general population, our findings pertain to patients with histologically confirmed CD. Lastly, our finding of an association of CD with vascular dementia might be due to chance in the context of multiple comparisons. Absent replication, this result should be interpreted with caution.

In conclusion, we found that CD is not associated with dementia risk, and that the increased risk of dementia within the first year of CD diagnosis was not seen in the longer term. Our finding of an increased risk of vascular dementia (and not Alzheimer's dementia) may be due to chance but does raise the possibility that vascular dementia may be a long-term consequence of CD analogous to the previously established risk of cardiovascular and cerebrovascular disease.

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SUPPLEMENTARY MATERIAL

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