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Research Submission

Risk of Headache-Related Healthcare Visits in Patients With Celiac Disease: A Population-Based Observational Study

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Background and Aims.—Patients with celiac disease (CD) are reported to be at increased risk for headaches, though large studies are lacking. We aimed to examine the risk of headache-related healthcare encounters in patients with CD in a nationwide population-based setting.

Methods.—In this population-based retrospective cohort study, we searched all (n = 28) pathology departments in Sweden and identified patients with CD based on the presence of villous atrophy (VA). Each patient was matched to up to 5 controls, by age, gender, calendar period, and region. Using Cox proportional hazards, we tested for an association between CD and subsequent headache-related visit. We also tested this association for those with intestinal inflammation but normal villi, and subjects with positive CD serologies but normal histology.

Results.—Among 28,638 patients with CD and 143,126 controls, headache-related visit occurred in 1,337 (4.7%) and 4,102 (2.9%), respectively. The incidence of headache-related visit was 423 per 100,000 person-years in CD patients and 254 per 100,000 person-years in controls (HR 1.66; 95% CI 1.56–1.77; $P < .0001$). Individuals having inflammation without VA on small intestinal biopsy (n = 12,898; HR 2.08; 95% CI 1.90–2.27; $P < .0001$) and those with normal mucosa but positive CD serology (n = 3,617; HR 1.83; 95% CI 1.57–2.12; $P < .0001$) were also at increased risk for headache-related visit.

Conclusions.—In this population-based study we found a significantly increased risk of headache-related visits in patients with CD; this increase was also present in patients with intestinal inflammation and those with positive CD serology but with normal mucosal architecture on small bowel biopsy. Though limited by surveillance bias, this study indicates that headache-related visits are more common in these populations.

Key words: celiac disease, headache, epidemiology

Abbreviations: CD celiac disease, CI confidence interval, GFD gluten-free diet, HR hazard ratio, VA villous atrophy

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INTRODUCTION

Celiac disease (CD) is an autoimmune disorder that is triggered in genetically predisposed individuals by the ingestion of gluten proteins in wheat, barley, and rye.[1] CD is characterized by small bowel mucosal inflammation and villous atrophy (VA), which results from exposure to dietary gluten and improves with the removal of gluten from the

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diet.[2] Although it was originally thought to be a rare malabsorption syndrome of childhood, CD is now known as a condition that can affect multiple organ systems and can be diagnosed at any age. CD is common in the general population, with an estimated worldwide prevalence of approximately 1%.[3] The prevalence of CD is somewhat higher in Sweden, approximately 1.8%.[4] The association between CD and neurologic disorders has been supported by numerous studies over the past 40 years. While peripheral neuropathy and ataxia have been the most frequently reported neurologic extra-intestinal manifestations of CD,[5,6] a growing body of literature has established headache as a common presentation of CD as well.[7,8] The exact prevalence of headache among patients with CD, however, remains unclear. While Cicarelli et al reported a 32% prevalence of migraines in 176 of their CD patients,[9] Briani et al found a prevalence of only 5.6% among 71 patients.[10] A more recent study of 188 patients with CD in the United States reported a 30% prevalence of chronic headaches.[11] To date, there have been no population-based studies examining the association between headache and CD.

The primary aim of this study was to investigate the frequency of headache-related office visits and hospitalizations in a nationwide population-based setting of patients with biopsy-proven CD. A secondary aim of this study was to assess the risk of headache-related visits in other patients without CD but with (1) intestinal inflammation without VA, and (2) normal mucosa but positive CD serology.

METHODS

Identification of CD Patients and Controls.—Details regarding this population-based database of patients diagnosed with CD have been described previously. [12,13] During the dates spanning October 27, 2006, and February 12, 2008 we searched the computerized biopsy registers at all 28 of pathology departments in Sweden to identify all individuals undergoing duodenal or jejunal biopsy from July 1969 to February 2008. Data were collected, including date of biopsy, biopsy site, morphology, and personal identity number.[14] Histologic findings were queried by Systematized Nomenclature of Medicine (SNOMED) codes. CD was defined as having VA, equivalent to Marsh histopathology grade 3. In a previous validation study involving medical record review of 114 patients with VA identified through this method, 95% had a clinical diagnosis of CD, with the most common presenting symptoms being diarrhea, anemia, weight loss, and abdominal pain.[12] For each patient with CD, the government agency Statistics Sweden identified up to 5 controls from the Total Population Register. This procedure was employed due to the consensus that little statistical efficiency is gained from matching more than 5 controls to each case.[15,16]

The following matching parameters were used: age, gender, year, and county of residence at the time of CD diagnosis. All matching was exact; age was matched by year (of diagnostic biopsy, or corresponding date for controls).

Measurement of Outcomes.—Headache-related healthcare encounters were defined as either an inpatient or outpatient visit with a relevant International Classification of Disease code in the Swedish Patient Register, which began in 1964 and became nationwide in 1987. Relevant codes are listed in Supporting Information Table S1. While the register only contained inpatient data prior to 2001, it has included both inpatient and hospital-based outpatient data since 2001. More than 99% of all medical care is registered in the registry, and most disorders have a positive predictive value of 85–95%.[17]

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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.

All individuals who had a headache-related visit prior to CD diagnosis or the corresponding date of inclusion as a control were excluded from the primary analysis. Therefore, all study participants were free of headache-related visit at study entry.

Educational Attainment.—Because socioeconomic factors may be associated with both a diagnosis of CD and headache, we adjusted for educational attainment. Education was divided in to four prespecified groups: ≤9 years of primary school, 2 years of high school, 3–4 years of high school, and college or university. In the case of children, the greater educational attainment of the subject's two parents was used.

Statistics.—The analysis of headache-related visit risk was conducted during the dates spanning March 1, 2015, and May 30, 2015. In our main analysis, we used Cox proportional hazards, conditioned on sex, age, and calendar year of study entry to measure for an association between CD and the subsequent development of headache. We tested the proportional hazards assumption by plotting log-minus-log curves and found that the curves were parallel. Time at risk began on the date of first biopsy with VA and on the corresponding index date in the matched controls, and time at risk ended at the development of headache, death, emigration, or December 31, 2009. We separately calculated the degree of association between CD and headache subtype (migraine, trigeminal neuralgia, and other/unclassified headache). All hazard ratios (HRs) were adjusted for educational attainment.

As the risk of headache-related visit in CD may change over time, we subsequently used CD status as a pseudo-time-dependent covariate (time after diagnostic biopsy or corresponding date for controls) to test whether the relationship between CD and headache remained constant over time after diagnosis.

In a series of sensitivity analyses, we retested for an association between CD and headache: (1) restricting headache-related visit definition to outpatient visits associated with this diagnosis; (2) restricting headache-related visit definition to at least two inpatient and/or outpatient visits; and (3) restricting headache-related visit definition to patients for whom headache was listed as the main diagnosis code for a medical visit.

Secondary Analyses.—So as to test for an association between headache-related visit and undiagnosed CD, and to assess for potential surveillance bias, we compared the proportion of individuals with a prior diagnosis of headache among those later diagnosed with CD to that of matched controls. We calculated odds ratios (ORs) using conditional logistic regression. These ORs were adjusted for education level.

So as to determine whether the risk of headache-related visit was specific to patients with CD, we also examined this association for patients with a lesser degree of mucosal damage, such as inflammation without VA (equivalent to Marsh grade 1–2) and normal mucosa (Marsh 0). Data on normal biopsies were sent for matching with CD serology at the biochemistry departments responsible for the same catchment areas as the hospitals at which the biopsies were obtained. In this manner, individuals with normal mucosa but positive CD serology at the time of biopsy (positive IgA/IgG gliadin, endomysium, or tissue transglutaminase antibodies) were identified. Patients with these conditions were matched to controls using the same criteria as enumerated above. While individuals with inflammation without VA originated from all Sweden, the third cohort consisting of individuals with normal mucosa but positive CD serology was regional and retrieved from the catchment areas of 8 university hospitals representing an estimated 49% of the Swedish population.[18]

We used SAS version 9.3 (Cary, NC, USA) for all analyses. We report hazard ratios (HRs) with corresponding 95% confidence intervals (CIs), and all reported *P* values are two-sided. This study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

RESULTS

Of 29,096 patients with CD and 144,527 matched controls, we excluded 458 CD patients and 1,401 controls who had a prior headache-related visit. Characteristics of the remaining CD patients

(n = 28,638) and matched controls (n = 143,126) are shown in Table 1. The median age of CD diagnosis was 30 years. Sixty-two percent of patients were female, and the majority of patients were diagnosed with CD after 1990. The median follow-up time for CD patients and controls was 9.95 years: 9.8 years for patients with CD and 10.0 years for controls. During the follow-up, 1,337 (4.7%) CD patients and 4,102 (2.9%) controls had a headache-related visit. This corresponded to an incidence of 423/100,000 person-years for the CD patients, and 254/100,000 person-years for the controls. A Kaplan-Meier plot of headache-free survival for CD patients and controls during the follow-up period is shown in Supporting Information Figure S1.

Overall and Time-Stratified Estimates.—There was a significant association between CD and headache-related visit (HR 1.66; 95% CI 1.56–1.77; $P < .0001$). This association was unchanged when we removed level of education from the model (unadjusted HR 1.66; 95% CI 1.56–1.77; $P < .0001$). Time-stratified analyses are shown in Table 2. The association was strongest in the first year after CD diagnosis (HR 2.42; 95% CI 1.92–3.04), but remained significant beyond 5 years after CD diagnosis (HR 1.54; 95% CI 1.42–1.66). As shown in Table 3, the association was similar for men and women and across calendar periods. When stratified by age, the relationship between CD and headache-related visit was present for all age categories except for age ≥80 years (see Table 3).

When we repeated the analysis, now restricting the definition of headache-related visit to outpatient visits associated with this diagnosis, this outcome occurred in 1,042 (3.6%) of CD patients and 3,329 (2.3%) controls; CD remained associated with the outcome of outpatient headache-related visit (HR 1.59 95% 1.48–1.70; $P < .0001$). Restricting the definition of headache-related visit to at least two medical visits (HR 1.83; 95% CI 1.65–2.03; $P < .0001$) continued to show a significant relationship between CD and headache-related visit. When restricting the outcome to headache as a primary diagnosis, headache-related visits occurred in 1,038 (3.6%) CD patients and 3,505 (2.5%) controls (HR 1.51; 95% CI 1.41–1.62; $P < .0001$).

Table 1.—Characteristics of Patients With Celiac Disease and Matched Controls

Characteristic	CD (n = 28,638)	Controls (n = 143,126)
Age at study entry (years)		
Mean/median/SD	32/30/25.8	32/30/25.7
0–19 (%)	11,720 (41)	58,662 (41)
20–39 (%)	5,211 (18)	26,034 (18)
40–59 (%)	6,332 (22)	31,800 (22)
60–79 (%)	4,726 (17)	23,548 (17)
≥80 (%)	649 (2)	3,082 (2)
Male (%)	10,954 (38)	54,589 (38)
Female (%)	17,684 (62)	88,537 (62)
Calendar period of study entry		
≤1989 (%)	4,076 (14)	20,324 (14)
1990–1999 (%)	11,936 (42)	59,533 (42)
≥2000 (%)	12,626 (44)	63,269 (44)
Mean/median follow-up time (years)	11.0/9.8	11.3/10.0
Headache-related visit (%)	1,337 (5)	4,102 (3)

Headache Subtypes.—When headache-related visits were classified by subtype (Table 4), 1,519 patients had visits related to migraine and 214 subjects had visits related to trigeminal neuralgia; 7 individuals had visits related to both migraines and trigeminal neuralgia. Migraine (HR 1.67; 95% CI 1.48–1.87; $P < .0001$) was significantly associated with a prior diagnosis of CD. This relationship was not significant for trigeminal neuralgia (HR 1.35; 95% CI 0.97–1.88; $P = .0776$). Those with unclassified headache-related visits had an association with

Table 2.—Association of CD With Subsequent Headache-Related Visit Stratified by Follow-Up Time

Stratum	Number of Events	Headache Incidence per 100,000 Person-Years	Adjusted* HR (95% CI)
Overall	1,337	423	1.66 (1.56–1.77)
<1 year	100	353	2.42 (1.92–3.04)
1–5 years	418	397	1.80 (1.62–2.01)
>5 years	819	448	1.54 (1.42–1.66)

*Compared with matched controls, adjusted for education level.

Table 3.—Association of CD With Headache-Related Visit Stratified by Gender, Age, and Year of Study Entry

Stratum	Number of Events	Headache Incidence per 100,000 Person-Years	Adjusted* HR (95% CI)
Overall	1,337	423	1.66 (1.56–1.77)
Gender			
Male	369	309	1.69 (1.50–1.90)
Female	968	492	1.65 (1.54–1.77)
Age at study entry (years)			
0–19	574	398	1.54 (1.40–1.69)
20–39	281	485	1.63 (1.42–1.86)
40–59	319	442	1.90 (1.67–2.15)
60–79	157	399	1.83 (1.53–2.20)
≥80	6	210	0.93 (0.38–2.29)
Calendar year of study entry			
1989 and before	185	220	1.52 (1.29–1.80)
1990–1999	631	402	1.61 (1.47–1.76)
2000 and after	521	692	1.80 (1.63–1.98)

*Compared with matched controls, adjusted for education level.

CD that was similar to that of migraine (HR 1.68; 95% CI 1.56–1.80, $P < .0001$).

Secondary Analyses.—When assessing the risk of headache-related visit prior to the diagnosis of CD, we found that headache-related visits were significantly associated with undiagnosed CD (OR 1.65; 95% CI 1.48–1.83; $P < .0001$). This relationship remained significant in all strata of sex and age (with the exception of age ≥80 years). The full results of this conditional logistic regression model are shown in Table 5.

Table 4.—Association of CD With Headache-Related Visit Subtype

Stratum	Number of Events	Headache Incidence Per 100,000 Person-Years	Adjusted* HR (95% CI)
Migraine	378	119	1.67 (1.48–1.87)
Trigeminal neuralgia	44	14	1.35 (0.97–1.88)
Other headache	916	290	1.68 (1.56–1.80)

Compared with matched controls, adjusted for education level.

When considering individuals with inflammation (Marsh grade 1–2) and those with positive serologies and normal intestinal biopsy, we found a significantly increased risk of headache-related visit among both of these groups (HR for inflammation 2.08; 95% CI 1.90–2.27; $P < .0001$, HR for positive serologies and normal biopsy 1.83; 95% CI 1.57–2.12; $P < .0001$).

DISCUSSION

This nationwide population-based study of more than 28,000 individuals with CD found a 1.66-fold increased risk of headache-related visit after a CD diagnosis as compared with matched controls. Furthermore, the association was bidirectional as those with a prior diagnosis of headache-related visit appeared to be at increased risk for a later diagnosis of CD. Headache subtype was available on a subset of patients, and our positive finding regarding migraine is congruent with the literature indicating that the most common diagnosis for headache-associated outpatient visits is migraine.[19] Similar to individuals with CD, there was a significantly increased risk of headache-related visit among those with small intestinal inflammation but no VA and those with normal mucosa but positive CD serology.

Our study showed that the association between headache-related visit and CD was similar in both genders, all calendar periods, and all but the highest age group. The finding that CD diagnosed at age ≥80 years was not associated with increased risk of headache-related visit likely reflects the epidemiology of headache, with an overall decline in prevalence at ages >65, and may also be due to the fact that older individuals who previously had headache were excluded from the analysis.[20]

Headache-related visits in our population occurred in 4.7% of patients with CD during a median follow-up time of nearly a decade. Although this cannot be directly compared with a point-prevalence estimate, headache as measured in this study appears to be significantly less common than the 30–32% point-prevalence of headache

Table 5.—Association of CD With Prior Headache-Related Visit (Conditional Logistic Regression)

Stratum	Number of Events	Prevalence of Prior Headache (%)	Adjusted* OR (95% CI)
Overall	458	1.6	1.65 (1.48–1.83)
Gender			
Male	137	1.2	1.77 (1.46–2.15)
Female	321	1.8	1.60 (1.42–1.82)
Age at study entry (years)			
0–19	82	0.7	2.19 (1.69–2.84)
20–39	101	1.9	1.50 (1.21–1.87)
40–59	145	2.2	1.61 (1.34–1.94)
60–79	119	2.5	1.69 (1.38–2.08)
≥80	11	1.7	0.95 (0.50–1.82)

*Compared with matched controls, adjusted for education level.

reported in two recent studies of patients with CD.[9,11] The reason for this discrepancy is likely in the nature of the outcome measured by each study. The studies by Cicarelli et al[9] and Dimitrova et al[11] utilized patient interviews and surveys, respectively, to assess for the presence of headache symptoms in patients with CD. No distinction was made between pre-existing headache and new symptoms following the diagnosis of CD. In contrast, Briani et al[10] prospectively monitored patients with histologically proven CD and measured the incidence of neurological symptoms at follow-up office visits. Similarly, the primary analysis in our study only counted diagnoses of headache that were made after a biopsy showing VA. Nevertheless, because individuals with headache may not seek medical attention, our measurement of headache-related visits underestimates the incidence of headache in both the CD and control groups. It is also possible that patients with CD, by virtue of their medical follow-up, may be more likely to be diagnosed with headache as compared with controls, and therefore surveillance bias may be contributing to the risk estimate.

While the mechanisms linking CD to headache are yet to be defined, some studies suggest that the inflammatory response in CD, including the upregulation of certain cytokines, may have a role.[21–24] In addition, both molecular mimicry and intermolecular help (a process by which immune reactivity to one molecule can trigger an immune response to another with which it is bound) have been proposed as potential mechanisms by which gluten ingestion can result in damage to the neuraxis, though considerable uncertainty remains.[25]

To our knowledge, this is the first study to also assess the risk of headache-related visits in individuals without VA on small intestinal biopsy, but rather inflammation (without VA), or normal mucosa but positive CD serology. We found that the risk of headache-related visits was increased among these other groups, and that they actually had a stronger association with the outcome of headache-related visits than that measured for CD. While these two groups of patients may actually represent either true CD patients with attenuated histology or patients with potential/latent CD who will ultimately progress to develop histologic inflammation and VA, it is also possible that they are affected by conditions other than CD. Numerous non-CD inflammatory and autoimmune conditions have been associated with small intestinal inflammation and positive CD serology,[18,26] and our findings may support the theory that there is a generalized inflammatory response that triggers headaches in these individuals. Though headache is commonly reported in patients with nonceliac gluten sensitivity,[11] our findings do not extend to this group, given the evolving diagnostic criteria for this clinical phenotype.[27]

Previous research has implicated certain inflammatory reactants, including CRP, MMP-9, cytokines, NF-kB, and iNOS, in the pathogenesis of headache.[21–24] A case series by Hadjivassiliou et al demonstrated an association between serum antigliadin antibodies, the presence of HLA-DQ2 (which was not measured in our study), and white matter lesions.[28] Furthermore, IgG antigliadin antibodies from human and animals have been shown to bind to human cerebellar tissue,[29] and to cross-react with synapsin I,[30] a protein involved in neurotransmitter release. Another potential

mechanism by which CD could cause headache is cerebral hypoperfusion, which has been reported to be more common in patients with untreated CD than treated CD.[31] This is further supported by vascular distribution of white matter abnormalities on neuroimaging seen in patients (with and without CD) with elevated antibodies to gliadin.[28] Whether inflammation, hypoperfusion, or both processes play a role in the pathogenesis of certain neurologic manifestations of CD, non-CD small intestinal inflammation, or CD seropositivity needs further investigation.

We found that the risk of headache-related visit in CD, while remaining increased, progressively declined over time (from <1 year to 1–5 years to >5 years from diagnosis). Adherence to the gluten-free diet was not measured in our study, and we, therefore, cannot conclude that this declining risk is due to a beneficial effect of that diet. Determination of the influence of the gluten-free diet on headache risk over time would be of interest, given several previous studies that found that this diet has positive effects on neurological symptoms in CD. In a longitudinal review of the clinical records of 140 patients, Cicarelli et al found not only a significant correlation between the duration of untreated CD and the number of neurological signs and symptoms, but also an inverse correlation between neurological abnormalities (including headache) and duration of dietary gluten restriction, consistent with our findings.[9] Similarly, Gabrielli et al showed that migraine patients with CD had either resolution of headaches or an improvement in the frequency, duration, and intensity of migraine within 6 months of initiating a GFD.[32] In a prior study, we found that the duration of GFD was not a predictor of headache severity in a surveyed population; however, in that study 8 of 39 CD patients with migraines reported complete resolution or great improvement in their headaches after initiation of GFD.[11]

A strength of this study is the nationwide population-based setting, which yielded a robust study population and high statistical power. Furthermore, our data sources have been previously validated. We obtained biopsy reports from all of Sweden's pathology departments, and it has been shown that 96–100% of all Swedish gastroenterologists and pediatricians during the study period reported performing a small intestinal biopsy before diagnosing a patient with CD.[12] Moreover, the biopsy report data on morphology used in this study were based on a mean of three tissue specimens, sufficient sampling to identify up to 95% of all CD.[18] We, therefore, have a very high sensitivity for diagnosed CD. With regards to the diagnosis of headache-related visit, the registry used in the study captured coding data for both inpatient and outpatient medical visits, and the accuracy of most diagnoses reported in the registry has previously been shown to attain 85–95% (though validation of these data for headache specifically has not been done).[17] Last, our long follow-up time (median of 9.95 years) allowed us to determine whether a diagnosis of CD affected the risk of headache-related visit during this time period, and it enabled us to stratify the analyses based on time from CD diagnosis.

We acknowledge a number of limitations. First, this study is subject to surveillance bias. The association we measured between CD and subsequent diagnosis of headache was likely influenced by the fact that entry into our study as an individual with CD was contingent on a small intestinal biopsy showing VA. Such patients with abnormal histopathology and a new diagnosis of CD are more likely to be carefully followed than the general population, increasing the likelihood of detecting concomitant medical conditions such as headache.

Second, it is possible that some of the reference individuals have undiagnosed CD. Given that the prevalence of CD in Sweden is 1–2%,[4] we believe that this is unlikely to significantly influence our risk estimates. In fact, such misclassification would be expected to decrease our HRs for headache-related visit. Along the same lines, the patient registry may have missed cases of headache due to inadequate or improper coding for medical visits, as well as the fact that headaches do not routinely require formal medical attention. It is likely, therefore, that our risk of headache-related visit was

actually underestimated. To ensure that all captured diagnoses of headache were accurate, we conducted sensitivity analyses restricting headache-related visit definition to at least two inpatient and/or outpatient visits and restricting headache definition to patients for whom headache was listed as the main diagnosis code for a medical visit. The results of these sensitivity analyses were consistent with our main risk estimates. Nevertheless, the reliance on claims codes for the measurement of the outcome is a limitation that is inherent to this study design, and the possibility of misclassification of the outcome remains.

Limitations of the patient registry also precluded us from reliably collecting data on known contributors to headache-related visits, including the use of medications such as nonsteroidal anti-inflammatory drugs, opioids, trazodone, contraceptives, and hormone replacement therapy. Similarly, although we were able to use inpatient and outpatient diagnosis codes to identify subtypes of headache-related visits, we were unable to measure headache frequency, duration, or intensity. Each of these characteristics may be impacted by a diagnosis of CD and subsequent institution of gluten-free diet, and this should be investigated in future research. Potential mediators of the relationship between CD and headache-related visits, such as depression, anxiety, obstructive sleep apnea, asthma, rhinitis, smoking status, and body mass index, were not available for this analysis. Finally, we performed multiple comparisons without correction for multiple testing and therefore these results should be considered exploratory until confirmed in future studies.

CONCLUSION

Individuals with CD seem to be at an increased risk of a headache-related visit compared with the general population. This risk persists over time from diagnosis but declines in magnitude. Similar to individuals with CD, there is a significantly increased risk of headache-related visit among those with small intestinal inflammation but no VA and those with normal mucosa but positive CD serology. The potential mechanisms by which autoimmunity, inflammation, and CD trigger headache should be investigated in future studies.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Fig. S1. Kaplan-Meier plot of headache-free survival in CD patients and controls.

Table S1. International Classification of Disease (ICD) Codes for *Migraine, Specified Headache, Non-Specified Headache, Trigeminal Neuralgia*