## **Review Article**

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# A systematic review and meta-analysis of the prevalence of celiac disease in migraine patients

## **Abstract**

**Background:** Celiac disease (CD) is a gluten-induced autoimmune disorder that can present with gastrointestinal, extraintestinal, or no symptoms. The prevalence of CD in migraine patients and the nature of their potential association is not well established. Therefore, the purpose of this study was to investigate the prevalence of CD in migraine patients using a systematic review and meta-analysis.

*Methods:* PRISMA guidelines created a framework for the construction of this review article. Two investigators independently searched the electronic databases of Scopus, PubMed, Web of Science and Google Scholar search engine up to May 2024. To assess heterogeneity among the studies, we used Cochran's Q test and the I² index. The statistical analyses were performed using Stata software, version 14.2, and a p-value of less than 0.05 was considered statistically significant.

**Results**: This meta-analysis included a total of 6 articles, comprising 14,526 migraine patients. The overall prevalence of CD in migraine patients was estimated to be (2% (95% CI: 0%-5%, I²=75.37, P=0.001)). Also, the Odds of CD disease in migraine patients compared to non-migraine patients was estimated to be equal (2.20 (95% CI: 0.87-5.54, I2=48.4, P=0.121)). Additionally, the majority of the research was conducted in Europe.

**Conclusions:** Although the small amount of research accomplished in this particular situation, our data indicate a relatively low prevalence of CD in migraine patients. Therefore, more frequent and thorough research in this field is advised. Patients with migraines experienced fewer attacks when they received gluten-free diets and were screened for celiac disease.

*Keywords:* Coeliac disease, Gluten sensitive enteropathy, Migraine, Systematic review, Meta-analysis.

#### Citation:

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**D**ecember 2019, CD is a small intestine-related chronic autoimmune digestive disease. This disease's symptoms are induced by consuming gluten-containing foods. CD can be serious, resulting in long-term digestive issues and preventing the body from receiving essential nutrients (1). The intestinal mucosa experiences crypt hyperplasia, villous atrophy, and intra-epithelial lymphocyte infiltration as a result of this immunological response (2). According to global statistics, CD affects one out of every 100 persons (3). CD can cause normal gastrointestinal symptoms like bloating or diarrhea, as well as rare extraintestinal manifestations including neurological issues or it can also be quiet or asymptomatic (4). On the other hand, throughout the last 40 years, several studies have found a link between CD and neurological diseases such as ataxia, peripheral neuropathy, and headache (5, 6). Additionally, a large number of people with migraine and neurological issues of unknown cause have tested positive for anti-gliadin antibodies (7-9). A throbbing headache that is usually unpleasant, migraines can also include photophobia, nausea, and vomiting (10-13).

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About 17% of women and 6% of men have experienced migraine attacks at some point in their lives, which significantly lowers their quality of life (14-16). According to research, headaches are a rare symptom of CD that responds favorably to a gluten-free diet (17, 18). Although the precise pathophysiology of migraine is not well known (19, 20), pro-inflammatory cytokines such as TNF- $\alpha$  and IL-1 $\beta$  are elevated in the blood of patients during migraine (21). Subsequently, the substances then impact the trigeminal nerve's pain receptors, which results in migraine attacks. Numerous studies have examined the connection between migraine and gastrointestinal conditions including CD and non-celiac gluten sensitivity (22-24), and each CD exhibits a pro-inflammatory response following gluten exposure and migraine (25).

Additionally, some studies indicate that migraine might be significantly reduced by treating the underlying GI disorder (for instance, CD patients may benefit from a gluten-free diet) (26, 27). According to an Italian study, CD was more common in migraine patients than in the control group (28). The initial issue to be covered by a number of original research and meta-analyses is whether migraine sufferers have a higher prevalence of celiac disease than the general population. This meta-analysis will be used to determine this. These patients will be invited to have a celiac screening test as part of the first laboratory testing if their prevalence of celiac disease is higher than that of the general population. Then, a series of case-control studies should be designed in the future to determine the number of attacks and severity of attacks in these migraine patients who receive a gluten-free diet compared to migraine patients who do not receive a gluten-free diet. Do they benefit from this diet or not? Several main epidemiological studies have been undertaken globally on the occurrence of CD in migraine patients (29, 30). In systematic review and

meta-analysis investigations, analyzing all of the documents and integrating them with the meta-analysis approach can provide a fuller picture of the dimensions of a societal problem (31, 32). Therefore, no systematic review and meta-analysis studies about the prevalence of CD in migraine patients were found by the study authors' search. Therefore, by conducting a comprehensive review of the existing literature, the current study aimed to determine the global prevalence of CD in migraine patients.

## **Methods**

The Standard Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were adhered to in this systematic review and meta-analysis (33).

Search strategy: We looked for English-language published publications without any date limitations using electronic databases including PubMed, Web of Science, Scopus, and Google Scholar search engine. The search included all literature published up to May 2024. The search technique included the MeSH keywords "Celiac disease" and "migraine". We scanned the reference lists of selected publications for more relevant articles. Additional, Appendix 1 (("Celiac Disease"[mesh] OR "Celiac Disease" [Title/Abstract] OR "Gluten Enteropathy" [Title/Abstract] OR "Gluten Enteropathies" [Title/Abstract] OR "Gluten Sensitive Enteropathy" [Title/Abstract] OR "gluten-induced enteropathy" [Title/Abstract] OR celiac\* [Title/Abstract] OR celiak\* [Title/Abstract] OR coeliac\* [Title/Abstract] OR coeliak\* [Title/Abstract] OR "non-tropical sprue" [Title/Abstract] OR "nontropical sprue" [Title/Abstract] OR "Celiac Sprue" [Title/Abstract] OR "coeliac disease" [Title/Abstract])) AND (("Migraine Disorders"[Mesh] OR Migraines [Title/Abstract] OR Migraine [Title/Abstract])) depicts the full search strategy for the PubMed database.

Table 1. Evaluation of the quality of studies based on the checklist Newcastle-Ottawa

id	Study	Selection	Comparability	Outcome	Score	Classification based on AHRQ standards
1	K. Griauzdaitė,	4	2	3	9	High
2	Maurizio Gabrielli,	3	2	2	7	High
3	Soroor INALOO	2	1	2	5	Moderate
4	Eli Lahat	3	2	2	7	High
5	Nike ZoeWelander	2	1	2	5	Moderate
6	F Alehan	4	2	1	7	High

Inclusion and exclusion criteria: Eligible studies included observational studies that reported the prevalence of CD or gluten intolerance or had compared probably CD in migraine patients and were published in English. Of course, Our search was not only specifically focused on the prevalence of celiac disease in migraine patients, but also on the relationship between migraine subtypes and CD, but no study had specifically examined any association between migraine subtypes and CD. Studies were excluded if they had the following criteria. 1) Studies did not have enough epidemiological information, 2) full-text was unavailable, and 3) sample size was not clearly stated.

Screening and data extraction: After deleting duplicate studies, two independent reviewers (NN and PJA) screened titles and abstracts to exclude unnecessary research. The reviewers extracted the data independently. A third reviewer (SHR) resolved any differences between the two primary reviewers. Data was entered into an Excel spreadsheet. Study characteristics (e.g., first author, published year, nation, study type, sample size, age, gender, and CD frequency) were among the extracted data.

Quality appraisal of the studies: The Newcastle-Ottawa Scale (NOS) checklist was used to evaluate the articles' quality (34). Three sections comprise the seven items in this checklist: 1) Comparability (one item); 2) Study selection (four items); and 3) Outcome (two items). The papers' whole content was examined by two authors (NN and PGA). Studies were classified as high-quality if their NOS ratings were seven or higher, as moderate if their scores were five to six, and as low if their scores were less than five, in which case they were eliminated from the meta-analysis (table 1).

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PGA). Studies were classified as high-quality if their NOS ratings were seven or higher, as moderate if their scores were five to six, and as low if their scores were less than five, in which case they were eliminated from the meta-analysis (table 1).

Statistical analysis: The pooled prevalence of celiac disease among migraine patients was calculated using the metaprop command. For studies that did not directly report an odds ratio (OR), the value was calculated using the formula OR = ad/bc, and the logOR was used to symmetrize the effect size. The standard error was derived as  $SE = [ln \text{ (upper 95\% CI - lower 95\% CI)}] / (2 \times 1.96)$ . Study heterogeneity was assessed using the  $I^2$  statistic and Cochran's Q test. A random-effects model was applied to estimate the pooled measures and their 95% confidence intervals when  $I^2$  exceeded 50%. Publication bias was evaluated by visual inspection of a funnel plot, and the influence of individual studies on the overall results was tested by sensitivity analysis, whereby each study was systematically removed and the model was re-calculated.

#### Results

**Selection of studies:** The search strategy to find the articles is shown in the PRISMA flow diagram (figure 1), which shows that out of the 1021 publications that were found, 959 were eliminated as duplicates or irrelevant based on the title and abstract. A full-text evaluation was conducted for the remaining 61 potentially articles, and following a thorough full-text review, 20 eligible articles were included in the analysis. Out of the 465 publications that were found, 141 were eliminated as duplicates or irrelevant based on the title and abstract, and 22 potentially articles were left. A total of 6 published studies that examined 14,526 patients were chosen for inclusion in this review after reported articles with titles that included CD prevalence indicators, review articles, editorials, and commentaries were removed. Table 2 summarizes the characteristics of the papers that are being provided.

Table 2. Summary of the study characteristics included in the systematic review

Author Year Reference	Continent	Country	N*(Mig raine)	Female /Male in migraine group	Age in migraine group Mean+SD	CD in migraine group	N (Contr ol)	Female /Male in control group	Age in control group Mean±SD	CD in control group
Griauzdaitė K, 2020 (35)	Europe	Lithuani	42	39/5	41.31	1				
Gabrielli M, 2003 (29)	Europe	Italy	90	63/27	37±8	4	236	147/89	35±9	1

Author Year Reference	Continent	Country	N*(Mig raine)	Female /Male in migraine group	Age in migraine group Mean+SD	CD in migraine group	N (Contr ol)	Female /Male in control group	Age in control group Mean±SD	CD in control group
Inalloo S, 2011 (30)	Asia	Iran	100	41/59	10.6±2.8	2	1500		9.5±1.3	30
Lahat E, 2000 (36)	Asia	Israel	41	23/18	9.5±1.6	0	34	14/20	6.5±0.6	0
Welander N.Z, 2021 (37)	Europe	UK	14180			86	47557 3			1973
Alehan F, 2008 (8)	Europe	Turkey	73	41/32	12.01±3.07	4	147	85/62	11.82±3.25	1

<sup>\*</sup>N=number

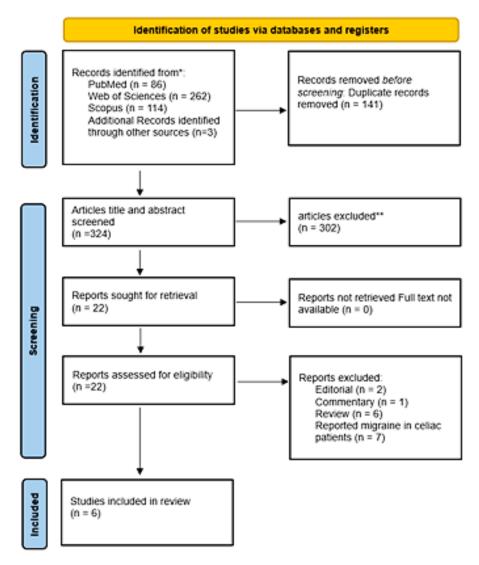


Figure 1. PRISMA flow diagram illustrating the identification and inclusion of studies in the systematic review and meta-analysis.

CD prevalence in migraine patients: Information about the prevalence of CD in migraine patients was available through six observational studies (8, 29, 30, 35-37), one study is excluded due to the presence of a zero fraction (36). As shown in figure 2-A, the overall prevalence of CD in migraine patients was 2% (95% CI: 0%-5%, I2=75.37, p<0.001). Also with random effect model, the four studies combined epidemiological data (14443 case group and 477456 control group) and the chance of having CD was found to be 2.20 higher in the migraine group than in the control group, although this difference was not statistically significant (2.20 (95% CI: 0.87-5.54, I2=48.4, P=0.121)) (figure 2-B).

CD prevalence in migraine patients by continent subgroup: Using the random effects model, four studies

from Europe and two from Asia were analyzed to determine the prevalence of CD in migraine patients. The findings showed that the prevalence of CD in migraine patients was equal in both regions, at 2% (95% CI: 0%-7%, I2=83.28, p<0.001) and 1% (95% CI: 0%-4%, I2=0, P=0.000), as shown in figure 3.

Sensitivity analysis demonstrated the impact of studies in meta-analytic research by demonstrating how their exclusion might either alter the results or have no effect at all on the ultimate direction. The overall conclusions of this analysis remained unaffected by the removal of one study. Additionally, using funnel plot as an examination for publication bias, it was determined that the effect is not significant (P=0.167) (figure 4).

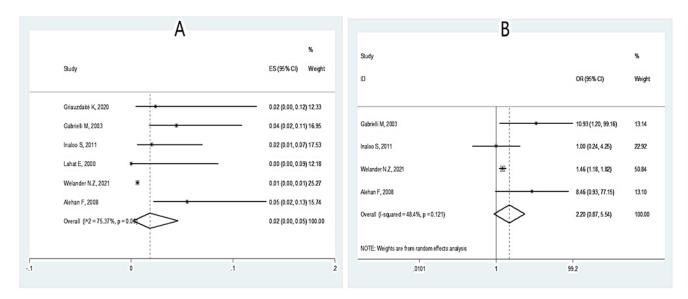


Figure 2. CD prevalence in migraine patients (A) and relationship between CD and migraine (B)

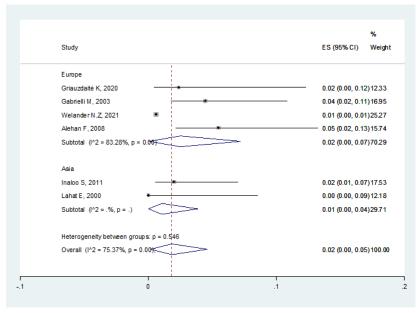
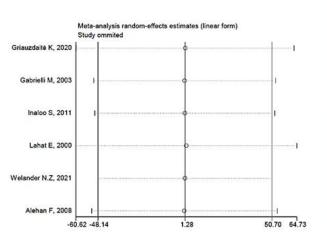


Figure 3. Prevalence of CD in the group with migraine according to the continent subgroup



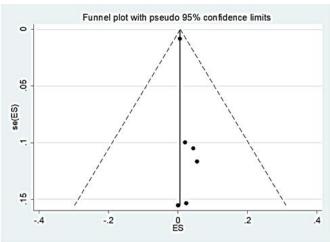


Figure 4. Sensitivity analysis and publication bias for CD prevalence studies in the migraine patients

#### **Discussion**

In comparison to people without migraines, this study is the first systematic review and meta-analysis to estimate the prevalence of CD in migraineurs and determine their risk of contracting the illness. According to the present study, the prevalence of CD in migraine patients was equal to 2%, and the chance of CD in migraine patients compared to nonmigraine patients was 2.20. There may be a pathophysiological difference for the substantial associations observed between migraine and peptic ulcers, Crohn's disease, ulcerative colitis, and CD (29). Also, the relationship between migraine and other diseases or autoimmune markers, such as rheumatoid arthritis (38) and some antiphospholipid antibodies (39) has been reported. This suggests that migraine may be related to autoimmunity in general. Some findings suggest that there may even be an autoimmune component in the pathophysiology of migraine (40). According to a meta-analysis study that investigated the chances of neurological diseases in people with CD, it showed that children with this disease may be at high risk of headache (41). Zeiss et al. conducted a comprehensive review and meta-analysis and highlighted that headache prevalence in CD patients is 18.3% in children and 26% in adults. Furthermore, it has been observed that up to 75% of CD patients had a complete diagnosis of headaches after GFD (42). This suggests that there is an inverse causal association between CD and migraine illness.

Although numerous theories have been mentioned, the actual mechanisms behind the correlation between CD and headache disorders are currently being investigated. A well-known etiopathogenetic theory links proinflammatory cytokines to the pathophysiology of CD and primary headache disorders, especially migraine (43). High serum

levels two well-established players pathophysiology of migraines, interleukin 1ß and tumor necrosis factor alpha, are commonly observed in migraine sufferers (44). It has been demonstrated that calcitonin gene-related peptide (CGRP), which is produced during migraine attacks and activated by cytokines, is found in over 50% of trigeminal ganglion neurons. These cytokines cause the trigeminal nerve to activate, transmitting pain signals( 45). In this instance, CD might be involved in the release of cytokines and, consequently, in the onset of headaches. In reality, in people with CD, gluten sets off an immune system overreaction that results in an inflammatory response and Tcell-mediated autoimmune enteropathy. association between CD and migraine may be explained by increased levels of TNF-α and interferon-gamma, which control the synthesis of CGRP.

The established relationship between dysbiosis and the gut-brain axis is another characteristic shared by CD and headache disorders. Indeed, a few researchers postulated that extraintestinal symptoms of CD may arise from the "environmental-microbial-epithelial-neural" brain network, which is akin to the "environmental-mucosal-ductal-neural" brain network (46). Furthermore, intestinal dysbiosis facilitates the release of lipopolysaccharides (LPS) into the bloodstream, which adds to the pro-inflammatory environment (43). It appears that the inflammatory reactions brought on by gluten ingestion are intimately linked to the beginning and worsening of headaches in people with CD. Gluten peptides have the ability to stimulate the immune system and release a series of cytokines and chemokines that promote inflammation. The blood-brain barrier is weakened by this inflammatory storm, which also makes it possible for cytokines brought on by gluten to enter the brain parenchyma and trigger headaches via neuroinflammatory pathways (47, 48). Recent research, however, has brought attention to the possible involvement of circulating autoantibodies to transglutaminase 6 in individuals who are susceptible to neurological conditions, such as headaches (49). Considering these results, more research into the interactions of autoimmune responses, proinflammatory cytokines, and genetic predisposition may shed light on the relationship between CD and headache disorders. There are four limitations to this study. First, the number of studies that investigated the prevalence of CD in migraine patients was small. Second, the epidemiological information of the studies was not enough and we could estimate the odds ratio for only four studies. Third, no study has specifically examined any association between migraine subtypes and CD. It seems that the odds CD is high in migraines compared to people without migraines, and its prevalence is about 2.20. Additionally, it should be taken into account that these data have been around for a long time and been confirmed by modifications in diagnostic recommendations. Even though only six researches have been done in this field, the majority of the given statistics are only partially credible when taking into account the most recent evidence on CD. Thus, more research on this subject is required.

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**Ethics approval:** Since no human nor animal subjects were used in this study, it is not applicable.

**Conflict of interests:** No conflicting interests are disclosed by the authors.

**Authors' contribution:** The authors of this article worked together to conduct this investigation. The study was planned and designed by GHK and SHR. PGA and N.N. conducted the search and gathered the information. The manuscript was edited by GHK, SHR, PGA, HGH, FF, and NN after SHR wrote the most of it. The final work has been read and accepted by all the authors, who also accept full responsibility for its content.

**Availability of data and materials:** Data can be provided to the creator of the correspondence. Naturally, table 2 contains a summary of the data from the article's text.

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