A CASE-CONTROL EPIDEMIOLOGICAL SURVEY ON POTENTIAL RISK FACTORS FOR CELIAC DISEASE

Matúš Bielik[1], Martin Selvek[2], Magda Suchánková[3], Ivana Shawkatová[3]
[1]Department of Internal Medicine II, Uherské Hradiště Hospital, Uherské Hradiště, Czech Republic
[2]Dôvera Health Insurance Company, Bratislava, Slovak Republic
[3]Institute of Immunology, Faculty of Medicine, Comenius University in Bratislava, Bratislava, Slovak Republic

SUMMARY

Objectives: Celiac disease (CD) is a chronic autoimmune disorder caused by a complex interplay between genetic and environmental factors. The main goal of our case-control study was to analyse the association of environmental factors with the odds of CD development in a sample of the Slovak population.

Methods: Data were collected from 1,226 respondents (534 CD patients and 692 controls) by a questionnaire. The impact of analysed parameters on the chance of disease development was assessed by multiple regression analysis and expressed as odds ratios (OR). Values of $p < 0.05$ were considered statistically significant.

Results: In the patient group, celiac disease was significantly more prevalent in women than in men (OR = 1.52, $p = 0.010$). Respondents with a positive family history of CD showed 2.9-fold higher odds of CD compared to others ($p < 0.001$), and respondents with coexisting autoimmune diseases had 2.6-fold higher odds of CD ($p < 0.001$). Subjects who had taken antibiotics at least three times a year during childhood had 1.95-fold higher odds of developing CD compared to those who took them less frequently or not at all ($p = 0.022$). Conversely, individuals who were breastfed in infancy had lower odds of CD compared to non-breastfed respondents (OR = 0.53, $p < 0.001$). The mode of delivery (vaginal vs. caesarean section), overcoming severe infections, and the timing of gluten introduction in childhood did not show a statistically significant effect on the odds of developing CD.

Conclusion: Based on our data, being female, having a positive family history of CD, suffering from another autoimmune disease, and frequent use of antibiotics are factors associated with an increased chance of developing CD. On the other hand, breastfeeding in infancy seems to have a protective effect. Our findings highlight the importance of further research in understanding the complexities of this autoimmune condition and providing a foundation for prevention strategies.

Key words: autoimmune disease, environmental factor, epidemiological survey, celiac disease, risk factor

Address for correspondence: I. Shawkatová, Institute of Immunology, Faculty of Medicine, Comenius University Bratislava, Odborárske nám. 14, 813 72 Bratislava, Slovak Republic. E-mail: ivana.shawkatova@fmed.uniba.sk

https://doi.org/10.21101/cejph.a8010

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder (AID) triggered by dietary gluten in genetically susceptible individuals of all ages. Lately, CD has emerged as a worldwide public health problem. It affects approximately 1% of the global population, however, it is more common in individuals of European descent and the prevalence is higher in females than in males (1–3).

Though CD primarily affects the small intestinal mucosa, the spectrum of clinical manifestations is very broad, including both intestinal and extraintestinal symptoms. The typical gastrointestinal symptomatology appears in the form of chronic diarrhoea, weight loss, bloating, abdominal discomfort, and malnutrition. Extraintestinal symptoms comprise a significant proportion of the clinical manifestation including among others osteoporosis, dermatitis herpetiformis, neuropsychiatric symptoms, infertility, anaemia, and thyroid dysfunction (4–6). However, the exact pathomechanisms underlying the diverse manifestations of the disease remain to be clarified.

Numerous studies have indicated that celiac disease is caused by a complex interaction between genetic and environmental factors that leads to an inappropriate immune response to gluten and eventually to the inflammation of the small intestine and characteristic villous atrophy and crypt hyperplasia (1, 7). It is well known that the key genetic determinants of CD are located in the human leukocyte antigen (HLA) region, with 95% of patients expressing molecules HLA-DQ2.5 (encoded by DQA1*05:01-DQB1*02:01 alleles) and the remainder HLA-DQ8 (encoded by DQA1*03:01-DQB1*03:02 alleles) or HLA-DQ2.2 (encoded by DQA1*02:01-DQB1*02:02 alleles). Genome-wide association studies identified also dozens of non-HLA loci that may be involved in CD development, most of which are shared with other immune-related diseases (8). The family of autoimmune disorders known to occur alongside celiac disease includes, e.g., type 1 diabetes, Crohn's disease, Hashimoto's thyroiditis, psoriasis, Graves' disease, and others (6, 9).

While genetic susceptibility is necessary for the development of celiac disease, it is not sufficient on its own, and environmental

factors are implicated in triggering the disease with exposure to gluten being the most crucial one. Several additional environmental conditions and dietary habits have been reported as potential risk factors for celiac disease such as the timing of gluten introduction, duration of breastfeeding, early childhood viral infections, alterations of the intestinal microbiome, and others (10–12). Understanding the impact of environmental factors on the development of celiac disease is essential for comprehending its multifactorial nature, identifying modifiable risk factors, and developing preventive strategies.

Therefore, the objective of our epidemiologic case-control study was to analyse the impact of potential risk factors on CD development in a sample of the Slovak population. We aimed to investigate the following factors: sex, family history of celiac disease, personal and/or family history of another autoimmune condition except for CD, mode of delivery, duration of breastfeeding, overcoming serious infections in childhood, use of antibiotics (ATB) in childhood, and age at gluten introduction into the diet.

MATERIALS AND METHODS

A total of 1,226 respondents participated in the survey, of whom 534 (43.6%) had celiac disease (patient group) and 692 (56.4%) were non-celiac subjects (control group). The average age of the respondents was 28.8 years, median 19.5, ranging from 3 to 66 years. The largest part of respondents was represented by young adults in the age category from 20 to 26 years (Fig. 1). The patient and control groups were roughly age- and sex-matched, while female respondents were overrepresented in both study groups (overall F:M ratio was 3:1). All participants were of Slovak descent.

Data collection was conducted through an online questionnaire using Google Forms, which was launched on 7 May 2021, and concluded on 4 June 2021. The survey consisted of questions regarding the epidemiological and clinical features of all participants, including their sex and age. Those who reported being diagnosed with celiac disease by a gastroenterologist also shared their age at diagnosis, with an average of 22.54 years. Further, all respondents were asked about the presence of other autoimmune diseases in their personal medical history and their immediate relatives with a request to additionally specify the type of AID. Inquiries about the mode of delivery (vaginal vs. caesarean), and breastfeeding (breastfed at least one month vs. formula) followed. Additionally, all participants were inquired about their history of significant childhood infections affecting the respiratory and gastrointestinal systems. To provide better clarity, the question included specific examples of these diseases such as laryngitis, otitis media, and rotavirus diarrhoea. The final questions were related to the frequency of antibiotic usage during childhood (in times per year), and the age (in months) at which gluten (like sponge biscuits, bakery, etc.) was introduced into the infant diet. To each question, there was an option to answer with "I do not know".

Potential respondents among adult celiac disease patients, non-celiac control individuals, and parents of paediatric CD patients and controls were randomly recruited from national patient organizations through social media. The diagnosis of CD in the patient group was established by gastroenterologists using standard criteria, which involved serological tests (as most patients have circulating antibodies against tissue transglutaminase), duodenal histology, and genetic testing. In children, European guidelines permit a diagnosis without a duodenal biopsy if symptomatic and serological criteria are met (13, 14).

Statistical Analysis

Differences between the two study groups in categorical variables were determined by the χ^2 test, whereas differences in continuous variables were assessed by the t-test or non-parametric equivalent in case of non-normal distributions. Multivariate logistic regression was used to model the probability of having celiac disease as a function of the risk factors. The use of dummy variables enabled the analysis of data from all respondents, including those who had not answered every question or chosen the option "I do not know". Odds ratios (OR) and 95% confidence intervals were computed for each risk factor enabling us to determine their impact on the chance of disease development. A p-value of less

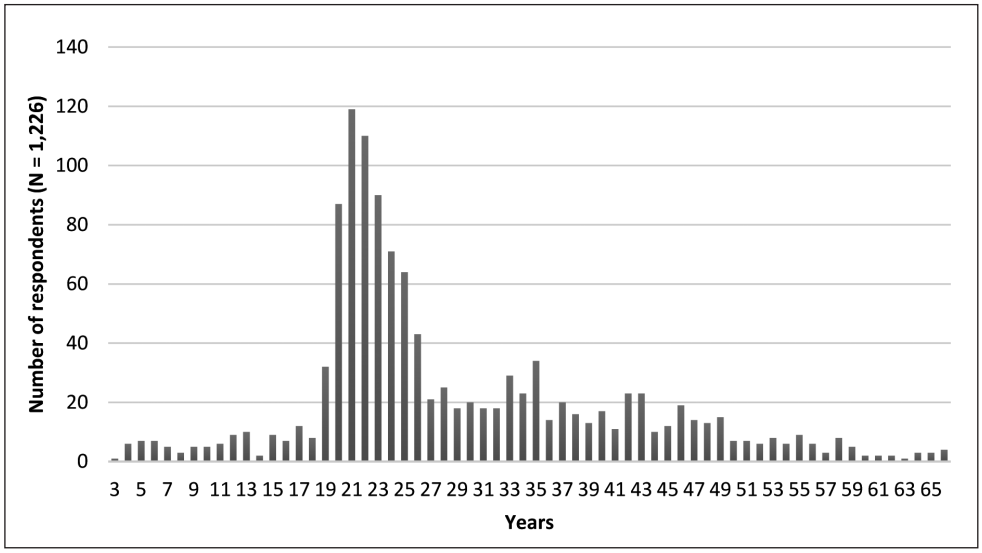

Fig. 1. *Age representation of survey respondents.*

than 0.05 was considered statistically significant. Analyses were run using the RStudio statistical package.

RESULTS

The representation of women in the CD patient group was statistically significantly higher compared to the control group, indicating that the female sex is a risk factor for disease development (OR = 1.521, p = 0.010), as demonstrated in Table 1.

Further, multivariate logistic regression analysis revealed that respondents with a positive family history of CD had 2.9-fold higher odds of developing celiac disease compared to respondents who had no close family members with CD (OR = 2.905, p < 0.001). The presence of another autoimmune disease in the respondent's personal history represented 2.6-fold higher odds of developing CD compared to those without any other AID (OR = 2.610, p < 0.001). The most common contemporaneous autoimmune disease in our survey was Hashimoto's thyroiditis. Out of 118 CD patients who provided a positive answer to this question, 55 (46.6%) had Hashimoto's disease compared to 25 out of 67 (37.3%) cases in the control group; data not shown.

The presence of other autoimmune diseases in the family history of the respondent, namely in first- and second-degree relatives, did not show a statistically significant effect on the chance of developing CD. Taking antibiotics more than 3 times a year during childhood increased the chance of developing CD by 96% compared to respondents who took antibiotics less frequently or not at all (OR = 1.958, p = 0.022). On the other hand, breastfed respondents had statistically significantly lower odds of developing CD compared to non-breastfed respondents (OR = 0.534, p = 0.001) signifying a protective effect of this factor. Among the individuals who were breastfed, the average period of breastfeeding was 8.63 months in the CD group compared to 6.81 months in the control group (p = 0.002). We did not find any association between the mode of delivery and the odds of developing CD (OR = 0.919, p = 0.672), indicating that whether the respondent was born vaginally or via caesarean section did not have a statistically significant impact on their likelihood of developing CD. As further given in Table 1, severe infections in childhood caused a

Table 1. *Impact of analysed parameters on probability of disease development*

Parameter	Category	Celiac disease patients n = 534	Controls n = 692	OR	95% CI	p-value
Intercept				2.767	1.313–5.876	0.008
Sex	Male	127	183	Reference		
	Female*	407	509	1.521	1.110–2.095	0.010
Family history of celiac disease	No	305	554	Reference		
	Yes*	229	138	2.905	2.189–3.870	< 0.001
Personal history of another autoimmune disease	No	416	625	Reference		
	Yes*	118	67	2.610	1.802–3.802	< 0.001
Family history of another autoimmune disease	No	348	526	Reference		
	Yes	186	166	1.297	0.968–1.737	0.081
Mode of delivery	Vaginal	451	593	Reference		
	C-section	77	85	0.919	0.618–1.357	0.672
	Unknown (DV)	6	14	0.767	0.223–2.315	0.652
Breastfeeding in infancy	No	97	68	Reference		
	Yes**	417	606	0.534	0.364–0.781	0.001
	Unknown (DV)	20	18	0.851	0.373–1.953	0.701
Severe infections in childhood	No	158	232	Reference		
	Yes	305	321	1.072	0.779–1.476	0.670
	Unknown (DV)	71	139	0.740	0.494–1.103	0.141
Frequency of taking antibiotics in childhood	Never	37	69	Reference		
	Less than once/year	145	266	0.872	0.520–1.481	0.607
	Once-twice/year	194	250	1.226	0.725–2.101	0.452
	More than 3 times/year*	158	107	1.958	1.106–3.511	0.022
Introduction of gluten into the diet	Within the first year of life	223	294	Reference		
	Within the first 6 months of life	183	181	0.831	0.611–1.130	0.237
	Unknown (DV)	128	217	0.641	0.451–0.911	0.013

Multiple regression analysis with dummy variables; CI – confidence interval; DV – dummy variable; OR – odds ratio; *statistically significant risk factor; **statistically significant protective factor

slightly higher (7.2%) likelihood of developing CD, however, the impact of this factor was not statistically significant (OR = 1.072, p = 0.670). Similarly, the timing of gluten introduction into the infant diet showed no statistically significant association with the development of CD in our study group (OR = 0.831, p = 0.237).

DISCUSSION

Celiac disease is an autoimmune condition where gluten consumption triggers an immune response leading to inflammation and damage to the small intestine. CD affects around 1% of the global population, with varying rates in different regions (3, 5). CD should not be confused with gluten intolerance, also known as non-celiac gluten sensitivity, involving adverse reactions to gluten without the autoimmune component (7). Non-celiac gluten sensitivity is more common, with estimates suggesting it may affect up to 6% of the world population. Distinct from celiac disease and gluten intolerance is wheat allergy – an allergic reaction to proteins in wheat, often involving symptoms like skin rash or gastrointestinal distress. The global incidence of wheat allergy is estimated to affect approximately 0.5% to 1% of the population, accounting for a notable portion of food allergies worldwide, especially among children.

A literature review reveals that the incidence of CD has increased significantly over the last decades (15). The observed increase in incidence is very unlikely to be caused by genetic factors highlighting the influence of environmental factors as well as the impact of improvements in diagnostic approaches (16). As given in Table 1, we have observed that in women the odds of developing CD were 52% higher compared to men. The higher prevalence of celiac disease in women in our study aligns with the findings reported in other countries with an estimated female-to-male ratio of 1.5–3:1 (2, 17).

Similarly, patients with a positive family history of CD had almost 3 times higher odds of developing the disease compared to patients whose immediate relatives do not have CD. Most studies support the statement that a positive family history represents an increased risk of developing CD, namely 6.3–8.8 times higher in first-degree relatives, and 1.3–5 times higher in second-degree relatives (18).

Based on our findings, patients who suffer from another autoimmune disease show 2.6 times higher odds of developing celiac disease compared to patients without a personal history of AID. The literature highlights an association of celiac disease with AID, particularly with type 1 diabetes, autoimmune thyroiditis, and some others, probably due to the shared genetic predisposition (2, 19). Generally, our observation corresponds with the well-known fact that CD patients have a significantly higher prevalence of autoimmune diseases in comparison to non-celiac individuals in the population (20).

Moreover, according to the results of our research, subjects who took ATB more than 3 times a year in childhood show significantly higher odds of developing CD compared to those who used ATB less frequently or did not use ATB at all. While earlier studies observed an increased risk of developing celiac disease caused by ATB use in the first year of life, particularly due to changes in intestinal microbiota (21), more recent research does not confirm this association. It seems that the recent findings do not support the hypothesis that avoiding the use of most types of antibiotics can be considered a preventive measure against the development of CD in children (1, 22). However, our observations indicate the opposite, and in our dataset, frequent use of antibiotics is associated with the development of celiac disease. It should be noted that data regarding ATB usage were self-reported and were not cross-checked with the patient's medical history.

Based on the above-given data, we can conclude that female sex, positive family history of CD, and the simultaneous occurrence of other autoimmune disorder(s) represent risk factors that significantly increase the risk of developing CD in genetically predisposed individuals consuming a diet containing gluten. Moreover, in contrast to some other recent studies, our data indicate also frequent use of ATB in childhood as a potential risk factor.

On the other hand, according to our findings, patients who were breastfed at least one month have lower odds of developing CD than patients who were not breastfed. These results are consistent with earlier literature, which considered breastfeeding and its length as significant factors affecting the development of CD in the sense of reducing the risk of disease development (3, 23). However, the latest data indicate that neither breastfeeding nor its duration can be considered a primary preventive factor for the development of CD (23). Nonetheless, these studies do not provide a clear indication of whether breastfeeding offers genuine protection in the short- or long-term or if it simply modifies symptoms, leading to delayed diagnosis as an outcome. The effect of breastfeeding on the development of CD is still a matter of debate.

In our study, we did not observe a statistically significant association between the development of CD and the mode of delivery, i.e., whether the patient was born vaginally or by caesarean section. Our findings align with other current studies where authors similarly agree that there is no confirmed link between caesarean delivery and an increased risk of developing CD (24, 25).

Infectious episodes have the potential to play a role in the development of CD, as they could increase gut permeability, leading to more efficient antigen penetration, and may also influence the immune system towards the Th1-type immune response characteristic of CD. According to our data, overcoming serious infections of the respiratory and gastrointestinal tract during childhood could have an impact on CD development, however, the observed association was not statistically significant. Current literature considers mainly viral infections (caused by adenoviruses, rotaviruses, reoviruses, and enteroviruses) as factors increasing the risk of developing CD (11). Our negative result could have occurred due to a relatively large number of respondents (17%) who indicated that they did not know whether they had overcome serious infections in childhood or not. Additionally, the terms "childhood" and "serious infection" were not sufficiently specified in the questionnaire, leading to potential ambiguity.

The timing of the introduction of gluten into the diet was not found to be a significant factor affecting the development of CD in our analysis. According to the current recommendations of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition from 2016, gluten should be introduced into the child's diet between the 4th and 12th month of age and no dietary measures can influence the absolute risk of developing CD. Other authors state that the timing and method of gluten introduction could play an important role in influencing the risk of disease development (26, 27).

The health burden of celiac disease is considerable because of its chronic course, the association with increased mortality and morbidity, restrictions in diet, and the related psychosocial stress. However, CD not only reduces the quality of life but also has extensive negative economic consequences. At present, the only effective treatment is a lifelong strict gluten-free diet. However, its compliance is often difficult to maintain due to the common presence of gluten not only among food additives but also in non-dietary sources (7). Moreover, while a gluten-free diet is generally effective in treating most individuals with CD, a substantial minority experiences persistent or recurrent symptoms despite adherence to the diet (6, 26). Therefore, the identification of at-risk subjects is vital for implementing effective prevention strategies tailored to each individual's needs.

Study Limitations

We are aware of several limitations of the study. One of them is the unequal representation of sexes among the respondents (25% of men vs. 75% of women). This limitation arises from the nature of questionnaire completion by respondents on social networks, where women seem to display generally higher activity than men. Another reason may be the fact that CD occurs more often in women, making this phenomenon more interesting to them compared to men.

As a limitation of the study, we can also consider the uneven age representation of the respondents, where the group of young adults under the age of 26 predominates. Celiac disease can develop at any age, from infancy to adulthood. However, it is most commonly diagnosed during early childhood (between 6 months and 2 years) or in people in their 20s and 30s. The average age at diagnosis in our study group was 22.54 years. The proportion of diagnosed CD patients was highest in the respondents under 20 years of age which could have biased our findings.

Finally, certain limitations of the study arise from the questionnaire-based nature of our epidemiological research which depends on the accuracy of respondents' answers to questions about breastfeeding and its duration, timing of gluten introduction into the diet, frequency of childhood antibiotic use, frequency of overcoming severe infections in childhood, and the occurrence of CD or other autoimmune diseases in the family. The respondents might not have precise information, or they could have provided it randomly and/or subjectively distorted.

CONCLUSION

Based on the results of our survey, being female, having a positive family history of celiac disease, suffering from another autoimmune disease, and frequent use of antibiotics in childhood are factors associated with an increased chance of developing celiac disease. On the other hand, our results show that breastfeeding in infancy may have a protective effect against the development of CD. Overall, our findings provide better insights into the risk factors for celiac disease in the Slovak population and potential prevention strategies.

Acknowledgement

We are very grateful to all respondents for their participation in the survey.

Conflicts of Interest

None declared

Adherence to Ethical Standards

Participation in the online survey was voluntary and all participants were informed about the nature and the purpose of the study. No personal data related to the identity of respondents were collected, therefore, data processing was conducted in a strictly anonymous manner.

REFERENCES

1. Tye-Din JA, Galipeau HJ, Agardh D. Celiac disease: a review of current concepts in pathogenesis, prevention, and novel therapies. Front Pediatr. 2018 Nov 21;6:350. doi:10.3389/fped.2018.00350.
2. Lindfors K, Ciacci C, Kurppa K, Lundin KEA, Makharia GK, Mearin ML, et al. Coeliac disease. Nat Rev Dis Primers. 2019 Jan;5(1):3. doi:10.1038/s41572-018-0054-z.
3. Singh P, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, et al. Global prevalence of celiac disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2018;16(6):823-36.
4. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA; American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013;108(5):656-77.
5. Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, et al. The Oslo definitions for coeliac disease and related terms. Gut. 2013;62(1):43-52.
6. Lebwohl B, Sanders DS, Green PHR. Coeliac disease. Lancet. 2018;391(10115):70-81.
7. Escudero-Hernández C, Peña AS, Bernardo D. Immunogenetic pathogenesis of celiac disease and non-celiac gluten sensitivity. Curr Gastroenterol Rep. 2016;18(7):36. doi:10.1007/s11894-016-0512-2.
8. Ciacchi L, Farenc C, Dahal-Koirala S, Petersen J, Sollid LM, Reid HH, et al. Structural basis of T cell receptor specificity and cross-reactivity of two HLA-DQ2.5-restricted gluten epitopes in celiac disease. J Biol Chem. 2022;298(3):101619. doi: 10.1016/j.jbc.2022.101619.
9. Emilsson L, Magnus MC, Størdal K. Perinatal risk factors for development of celiac disease in children, based on the prospective Norwegian Mother and Child Cohort Study. Clin Gastroenterol Hepatol. 2015;13(5):921-7.
10. Ivarsson A, Myléus A, Norström F, van der Pals M, Rosén A, Högberg L, et al. Prevalence of childhood celiac disease and changes in infant feeding. Pediatrics. 2013 Mar;131(3):e687-94.
11. Stene LC, Honeyman MC, Hoffenberg EJ, Haas JE, Sokol RJ, Emery L, et al. Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: a longitudinal study. Am J Gastroenterol. 2006;101(10):2333-40.
12. De Palma G, Nadal I, Medina M, Donat E, Ribes-Koninckx C, Calabuig M, et al. Intestinal dysbiosis and reduced immunoglobulin-coated bacteria associated with coeliac disease in children. BMC Microbiol. 2010 Feb 24;10:63. doi: 10.1186/1471-2180-10-63.
13. Calado J, Verdelho Machado M. Celiac disease revisited. GE Port J Gastroenterol. 2022;29(2):111-24.
14. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012 Jan;54(1):136-60.
15. Lerner A, Jeremias P, Matthias T. The world incidence of celiac disease is increasing: a review. Int J Recent Sci Res. 2015;6(7):5491-6.
16. Bergman D, King J, Lebwohl B, Clements MS, Roelstraete B, Kaplan GG, et al. Two waves of coeliac disease incidence in Sweden: a nationwide population-based cohort study from 1990 to 2015. Gut. 2022;71(16):1088-94.
17. Jansson-Knodell CL, Hujoel IA, West CP, Taneja V, Prokop LJ, Rubio-Tapia A, et al. Sex difference in celiac disease in undiagnosed populations: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2019;17(10):1954-68.
18. Faye AS, Polubriaginof F, Green PHR, Vawdrey DK, Tatonetti N, Lebwohl B. Low rates of screening for celiac disease among family members. Clin Gastroenterol Hepatol. 2019;17(3):463-8.
19. Vidan-Jeras B. When type 1 diabetes meets celiac disease. HLA. 2018 Dec;92 Suppl 2:64-6.

20. Conti L, Lahner E, Galli G, Esposito G, Carabotti M, Annibale B. Risk factors associated with the occurrence of autoimmune diseases in adult coeliac patients. Gastroenterol Res Pract. 2018 Sep 12:2018:3049286. doi: 10.1155/2018/3049286.
21. Canova C, Zabeo V, Pitter G, Romor P, Baldovin T, Zanotti R, et al. Association of maternal education, early infections, and antibiotic use with celiac disease: a population-based birth cohort study in northeastern Italy. Am J Epidemiol. 2014;180(1):76-85.
22. Kemppainen KM, Vehik K, Lynch KF, Larsson HE, Canepa RJ, Simell V, et al. Association between early-life antibiotic use and the risk of islet or celiac disease autoimmunity. JAMA Pediatr. 2017;171(12):1217-25.
23. Vieira Borba V, Sharif K, Shoenfeld Y. Breastfeeding and autoimmunity: programing health from the beginning. Am J Reprod Immunol. 2018;79(1). doi: 10.1111/aji.12778.
24. Dydensborg Sander S, Hansen AV, Størdal K, Andersen AN, Murray JA, Husby S. Mode of delivery is not associated with celiac disease. Clin Epidemiol. 2018;10:323-32.
25. Lionetti E, Castellaneta S, Francavilla R, Pulvirenti A, Catassi C; SIGENP Working Group of Weaning and CD Risk. Mode of delivery and risk of celiac disease: Risk of Celiac Disease and Age at Gluten Introduction cohort study. J Pediatr. 2017 May;184:81-6.
26. Meijer C, Shamir R, Szajewska H, Mearin L. Celiac disease prevention. Front Pediatr. 2018 Nov 30;6:368. doi:10.3389/fped.2018.00368.
27. Szajewska H, Shamir R, Mearin L, Ribes-Koninckx C, Catassi C, Domellöf M, et al. Gluten introduction and the risk of coeliac disease: a position paper by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2016;62(3):507-13.

Received August 12, 2023
Accepted in revised form April 16, 2024