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META-ANALYSIS

Prevalence and etiologies of non-responsive celiac disease: A systematic review and meta-analysis

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gluten-free diet, malabsorption, refractory celiac disease.

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Author contribution: N. A., P. S., and G. K. M. completed the study design. Literature search and data extraction were carried out by N. A., U. B., and A. D. S. Assessment of quality of included studies was carried out by N. A., U. B., and A. D. S. under the supervision of V. D., P. S., and G. K. M. Qualitative synthesis was carried out by all authors. Data analysis was performed by N. A. and V .D. A. D. S., P. S., and G. K. M. consulted on the analysis. All authors were involved in the interpretation of the results. N. A. and U. B. created the figures. N. A. drafted the initial manuscript. The manuscript was revised by N. A., U. B., A. D. S., P. S., and G. K. M. and approved for final submission by all authors.
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Abstract

Background and Aim: Non-responsive celiac disease (NRCD) is defined as ongoing symptoms despite 6–12 months of gluten-free diet (GFD), the only known treatment for celiac disease (CeD). There is inconsistency in studies describing the proportion of patients having NRCD and its various causes among patients with CeD. We therefore conducted a systematic review and meta-analysis to determine the prevalence and causes of NRCD.
Methods: The PubMed, Embase, Cochrane Library, Scopus, and Web of Science databases were searched for original studies reporting the proportion of patients with persistent symptoms after ≥ 6 months of GFD. Studies reporting the etiologies of NRCD were also identified. The systematic review was conducted as per the Meta-analysis of Observational Studies in Epidemiology guidelines. Statistical analysis was performed in STATA.
Results: Of 2965 search results, nine studies met the inclusion and exclusion criteria. Five studies (n = 4414) reported data on prevalence, and seven studies (n = 790) reported the causes of NRCD. The pooled prevalence of NRCD was 22% (95% confidence interval, 11–35%). Among patients with NRCD, inadvertent exposure to gluten was the most common cause (33%), followed by functional gastrointestinal disorders including irritable bowel syndrome in 16%. Refractory CeD type II along with its premalignant and malignant sequelae was observed in 7% of patients with NRCD.
Conclusion: One in five patients with CeD may not respond to GFD and would likely be classified as NRCD. Inadvertent gluten exposure was the cause of ongoing symptoms in one-third of patients with NRCD. Improving adherence to GFD along with developing novel therapeutics to mitigate symptoms due to ongoing gluten exposure is critical.

Introduction

Celiac disease (CeD) is one of the most common causes of enteropathy, and at least 0.7% of the global population have biopsy-confirmed CeD.[1] While gluten-free diet (GFD) is the only effective treatment for CeD, several therapeutic approaches and targets are undergoing clinical trials.[2,3] The response to GFD and adherence to GFD is highly variable, and a significant proportion of patients continue to exhibit clinical symptoms despite maintaining a GFD. Patients with CeD having a lack of initial response to GFD even after 6–12 months of GFD or recurrence of symptoms in a patient who initially responded to GFD despite continued dietary adherence are defined as non-responsive CeD (NRCD).[4–7] There are several known causes that lead to NRCD including persistence of gluten exposure (inadvertently or advertently), small intestinal bacterial overgrowth (SIBO), microscopic colitis, irritable bowel syndrome (IBS), and refractory CeD (RCD).[5–10] Among all, RCD is the most concerning cause of NRCD, which is defined as persistent signs and symptoms of CeD despite a strict GFD, as confirmed by a dietician, in the absence of other causes of NRCD or overt malignancy.[11,12] Based on the immunophenotyping of intraepithelial lymphocytes (IELs) and clonality of T-cell receptors (TCRs), RCD may be

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classified into two types: type I, which tends to follow a more benign course, and type II RCD, which has an elevated risk of progression to enteropathy-associated T-cell lymphoma (EATL).[13,14]

The data of recent studies have been inconsistent in defining the proportion of NRCD among patients with CeD.[5,6,8,15,16] There is also a significant heterogeneity in the prevalence of various causes of NRCD described earlier. The majority of pharmacological therapies being developed for CeD are likely to target patients with NRCD (or its subpopulation such as those with persistent gluten exposure); understanding the global burden of NRCD and the etiology of NRCD is extremely important. Therefore, we conducted a systematic review and meta-analysis to determine the pooled prevalence of NRCD among patients with CeD as its primary objective and to pool the proportions of different causes of NRCD as its secondary objective.

Methods

For the present systematic review, we followed the guidelines laid down by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The PRISMA checklist has been enclosed in the supporting information.

Database search. The PubMed, Embase, Cochrane Library, Scopus, and Web of Science databases were searched for relevant articles using various combinations of the terms "celiac OR coeliac," "gluten-free diet OR GFD," and "non-respon* OR partial respon* OR 'persistent symptoms' OR 'lack of response'." The detailed search strategy has been mentioned in the supporting information. Because the modern guidelines for diagnosis of CeD were released by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines in the year 1990, all original articles published after the year 1990, up until May 19, 2023, were included in the current study.

Definitions. In the present systematic review, the diagnosis of CeD was established on the basis of positive anti-tissue transglutaminase antibodies (anti-tTG Ab) and/or anti-endomysial antibodies (anti-EMA Ab) and the presence of villous abnormality on duodenal biopsy. The diagnosis of CeD was also made in the presence of high anti-tTG Ab titers (≥ 10×) with the presence of anti-EMA Ab.[17] NRCD was defined as patients with CeD with persistent clinical manifestations despite reported adherence to GFD for at least 6 months.[4–6]

Eligibility for inclusion. The criteria for inclusion of studies in this systematic review were (i) studies published in the English language after the year 1990, (ii) availability of the full-text articles, (iii) studies involving inclusion of consecutive patients with CeD, (iv) adherence to GFD for at least 6 months, and (v) use of established criteria for diagnosis of CeD and NRCD.

We excluded the following studies: (i) conference abstracts where full text was not available for review; (ii) studies published in a non-English language; (iii) studies involving a biased sampling of CeD patients, such as studies only including patients with CeD who underwent a repeat endoscopic biopsy; and (iv) non-human studies.

Selection of the studies. After manual removal of duplicates, the search results were independently screened by two reviewers (N. A. and A. D. S.) on the basis of title and abstract to assess for their inclusion in the present study. If found suitable, full-text articles were retrieved for further screening. If a consensus was not reached between the two reviewers, then a third reviewer (G. K. M.) was involved to reach a final decision.

Data extraction. Among the included studies, relevant data were extracted independently by two reviewers (N. A. and A. D. S.): first author, year of publication, country where study was conducted, sample size, patient characteristics, criteria used to define CeD and NRCD, duration of GFD, and the proportion of individuals with NRCD or specific causes of NRCD, if available.

Quality assessment of included studies. The quality of included studies was assessed independently by two reviewers (N. A. and U. B.) using the Newcastle–Ottawa Scale for cross-sectional studies. In case of any disagreement, a final decision was reached in consensus with a third reviewer (P. S. or G. K. M.).

Outcomes. The primary outcome of our study was the pooled prevalence of NRCD in patients with CeD on a GFD for a minimum of 6 months. The secondary outcomes were the etiologies of NRCD and their pooled proportions among patients with NRCD.

Statistical analysis. The extracted data were entered into Microsoft Excel and were analyzed using STATA version 14 (StataCorp, College Station, TX, USA). Before pooling the prevalence estimates, the variance was stabilized using the Freeman–Tukey transformation. All the estimates are presented after back-transformation. A random-effects meta-analysis model was used to calculate the overall pooled prevalence. Publication bias was detected qualitatively by visual inspection and quantitatively by Begg's test. The prevalence of the causes was estimated by similar methods. Heterogeneity was assessed statistically using the I^2 test.

Subgroup analyses were performed to identify and explain potential sources of heterogeneity. The a priori hypotheses to explain heterogeneity were that it was due to differences in age of study participants, duration of GFD, and region (i.e. differences among continents).

Results

Results of the search. Using the search strategy and after removal of duplicates, 2965 search results were identified from PubMed, Embase, the Cochrane Library, Scopus, and Web of Science databases. The details and outcome of the literature review have been summarized as a PRISMA flow diagram (Fig. 1). After using the inclusion and exclusion criteria detailed earlier, a total of nine studies were included in the final analysis.[5–10,15,16,18]

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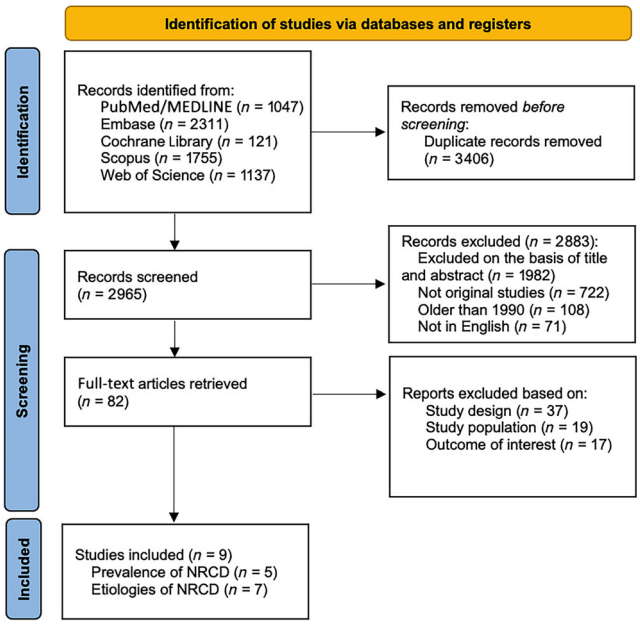


Figure 1 Flow diagram outlining our study selection process. NRCD, non-responsive celiac disease.

Table 1 Characteristics of included studies

Studies reporting the prevalence of NRCD

Author (year)	Country	Study design	Inclusion criteria	Duration of GFD	n_1
Penny *et al.* (2022)[8]	UK	Single-center, ambispective	Age ≥ 16 years	≥ 12 months	2553
Vuolle *et al.* (2022)[15]	Finland	Single-center, prospective	Age ≥ 18 years, diagnosed with CeD at age < 18 years	—	239
Veeraraghavan *et al.* (2021)[5]	USA	Single-center, retrospective	Age < 18 years	≥ 6 months	616
Sansotta *et al.* (2018)[16]	USA	Single-center, retrospective	Both children < 18 years and adults ≥ 18 years	≥ 24 months	513
Leffler *et al.* (2007)[6]	USA	Single-center, retrospective	—	≥ 6 months	603

Studies reporting the etiology of NRCD

Author (year)	Country	Study design	Inclusion criteria	Duration of GFD	n_2
Penny *et al.* (2022)[8]	UK	Single-center, ambispective	Age ≥ 16 years	≥ 12 months	285
Veeraraghavan *et al.* (2021)[5]	USA	Single-center, retrospective	Age < 18 years	≥ 6 months	91
van Wanrooij *et al.* (2017)[9] ≥ 12 months	The Netherlands 92	Single-center, prospective	—		
Stasi *et al.* (2016)[10]	Italy	Single-center, prospective	Age ≥ 18 years	≥ 12 months	56
Dewar *et al.* (2012)[18]	UK	Single-center, prospective	Age > 18 years	—	112
Leffler *et al.* (2007)[6]	USA	Single-center, retrospective	—	≥ 6 months	99
Abdulkarim *et al.* (2002)[7]	USA	Single-center, prospective	Age ≥ 21 years	≥ 12 months	55

CeD, celiac disease; GFD, gluten-free diet; n_1, total number of patients in the study; n_2, number of patients who underwent workup for etiology of NRCD; NRCD, non-responsive celiac disease.

Characteristics of the included studies. The nine studies included in the meta-analysis were single-center studies published between 2002 and 2022 across two continents and five countries (Table 1), with most studies published from the USA[5–7,16] and others from Europe (including Finland,[15] Italy,[10] the UK,[8,18] and the Netherlands[9]).

Most of the studies reported data on adult patients with CeD,[7,8,10,15,16,18] while two studies[5,16] also included adolescents and children. One study did not report the age limit in the inclusion criteria.[6] In the studies that reported demographic data on patients with NRCD, most of the patients were female.[5,6,8,10,15,18] Three studies did not report the gender of patients with NRCD.[7,9,16]

The included studies had used serological and histopathological evidence for the diagnosis of CeD. Most of the studies involved patients after a minimum trial of 12 months of GFD before they were evaluated for NRCD.[7–10] Other studies used a duration of 6 months[5,6] or 24 months of GFD.[16] Adherence to GFD was assessed by history/questionnaires,[7,10,15,16] dietician

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assessment,[5–7,9] serology,[7,9,16] or a combination of these; two studies did not report how the compliance with GFD was assessed.[8,18] Five studies[5,6,8,15,16] reported the proportion of patients with NRCD among the CeD patients, while seven studies reported the causes of NRCD.[5–10,18]

Results of quality assessment of included studies. Using the Newcastle–Ottawa Scale, three[5,15,16] and six[6–10,18] of the included studies were noted to be at a low and medium risk of bias, respectively. Detailed quality assessment has been included in the supporting information.

Quantitative data synthesis

Pooled prevalence of non-responsive celiac disease. The prevalence of NRCD among the included studies ranged from 12.5% to 50%.[5,6,8,15,16] The pooled prevalence of NRCD in five eligible studies including 4414 patients was 22% (95% confidence interval [CI], 11–35%; I^2 = 98.6%; Fig. 2).[5,6,8,15,16] No publication bias was observed on the funnel plot or the Begg's test (P = 0.13).

Pooled prevalence of non-responsive celiac disease by subgroups

Duration of gluten-free diet. The prevalence of NRCD did not change with the duration of GFD from 6 *versus* 12–24 months (17% [95% CI, 4–20%][5,6,15] *vs* 17% [95% CI, 16–18%],[8,16] P = 1.00) (Table 2). However, studies reporting prevalence of NRCD in patients on GFD for 6 months had higher heterogeneity compared with those reporting prevalence of NRCD among patients on GFD for 12–24 months (I^2 = 50% *vs* 0%, respectively).

Adults *versus* children. Similarly, studies reporting the prevalence of NRCD among the adult population had much higher heterogeneity compared with those reporting it in children (I^2 = 99.1% *vs* 0%, respectively). However, the prevalence of NRCD among adults and children was similar (28% [95% CI, 6–59%][8,15,16] *vs* 21% [95% CI, 18–24%], P = 0.62).[5,16]

Geographical regions. On analyzing by continent, there was no difference in the pooled prevalence of NRCD among patients from North America (USA) (27% [95% CI, 10–49%]; I^2 = 98.9%; three studies,[5,6,16] n = 1681) *versus* Europe (UK and Finland) (13% [95% CI, 12–14%]; I^2 = 0; two studies,[8,15] n = 2733) (P = 0.16). Subgroup analysis could not be performed by gender as the data on men and women with CeD were not reported separately in the included studies.

Etiologies of non-responsive celiac disease. Among the studies that reported the causes of NRCD (seven studies,[5–10,18] n = 790), the most common cause of NRCD was observed to be inadvertent exposure to gluten in 33% (95% CI, 27–39%;

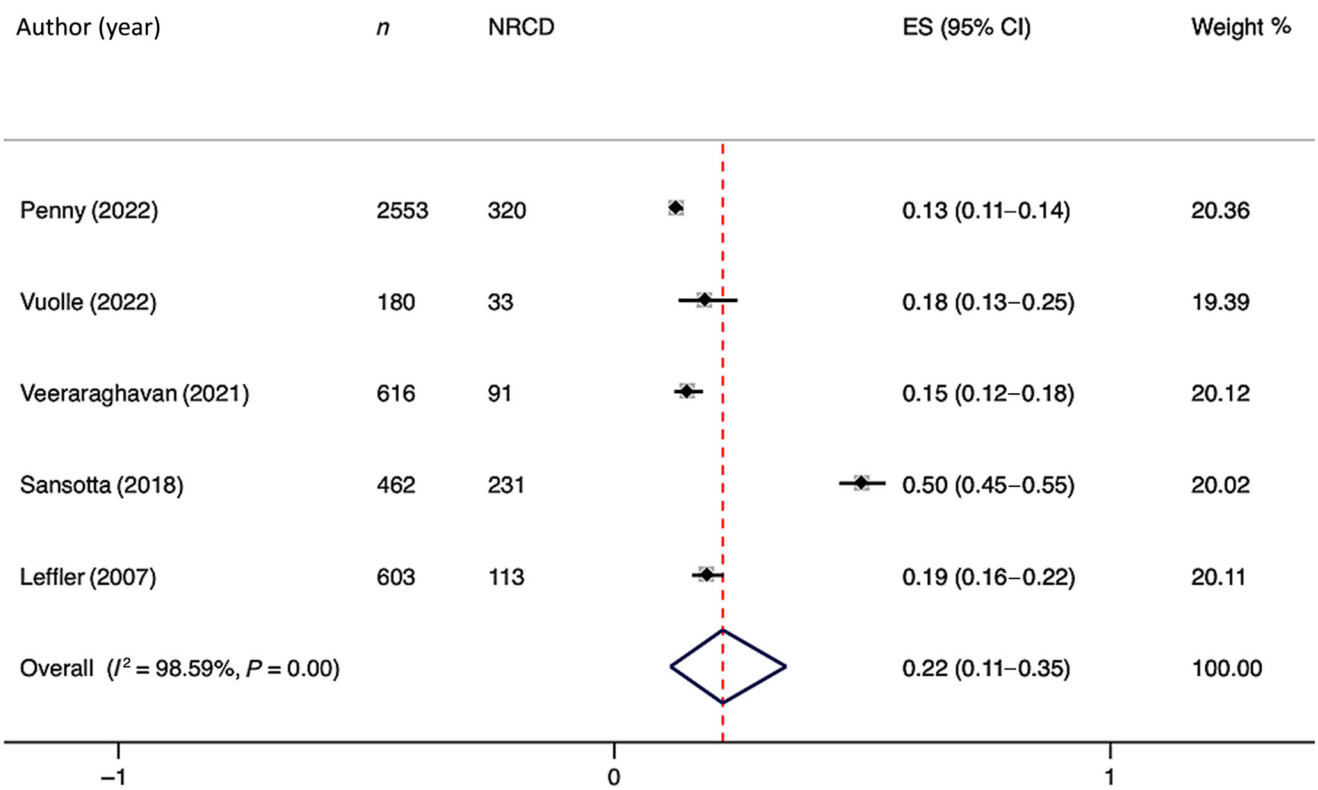


Figure 2 Forest plot depicting pooled prevalence of non-responsive celiac disease (NRCD). CI, confidence interval; ES, effect size.

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Table 2 Results of sensitivity/subgroup analysis

Studies included in subgroup	Studies	*n*	Prevalence (% [95% CI])	I^2	*P*-values
Pooled global prevalence of NRCD	Five[5,6,8,15,16]	4414	22% (11–35)	98.6%	
Based on continent of study					
North America (USA)	Three[5,6,16]	1681	27% (10–49)	98.9%	0.16
Europe (UK, Finland)	Two[8,15]	2733	13% (12–14)	0	
Based on age of included patients					
Adults (age ≥ 18 years)	Three[8,15,16]	2957	28% (6–59)	99.11%	0.62
Children (age < 18 years)	Two[5,16]	854	21% (18–24)	0	
Based on duration of GFD prior to diagnosis of NRCD					
6 months	Three[5,6,15]	1399	17% (14–20)	46.96%	1
12–24 months	Two[8,16]	3015	17% (16–18)	0	

CI, confidence interval; GFD, gluten-free diet; NRCD, non-responsive celiac disease.

Table 3 Etiologies of NRCD

Etiology	Studies	*n*	Prevalence	I^2
Gluten exposure	Seven[5–10,18]	790	33% (27–39)	64.3%
IBS, functional diarrhea	Seven[5–10,18]	678	16% (11–22)	76.7%
RCD type I	Five[5,8–10,18]	636	5% (0–15)	94.7%
RCD type II (also includes ulcerative jejunitis, lymphoma, and small bowel adenocarcinoma)	Seven[5–10,18]	790	7% (2–13)	88%
Small intestinal bacterial overgrowth	Four[6–8,18]	551	6% (2–12)	74.9%
Microscopic colitis	Six[5–9,18]	734	6% (3–10)	71.2%
Lactose/fructose intolerance	Six[5–8,10,18]	698	5% (3–8)	45.6%
Inflammatory bowel disease	Four[6,8,9,18]	588	2% (0–4)	61.1%
Miscellaneous	Seven[5–10,18]	790	12% (5–21)	91.2%
Undetermined	Three[5,8,10]	432	7% (0–23)	94.4%
Incorrect diagnosis	Four[7,9,10,18]	315	7% (4–12)	45.1%

IBS, irritable bowel syndrome; NRCD, non-responsive celiac disease; RCD, refractory celiac disease.

I^2 = 64.3%). This was followed by IBS (16% [95% CI, 11–22%; I^2 = 76.7%]; seven studies,[5–10,18] *n* = 790). RCD type 1 was observed in 5% (95% CI, 0–15; I^2 = 94.7%; five studies,[5,8–10,18] *n* = 636) of patients with CeD, while RCD type II and its malignant sequelae were noted in 7% (95% CI, 2–13%; I^2 = 88%; seven studies,[5–10,18] *n* = 790) of patients (Table 3).

The other less frequent causes of NRCD were SIBO (6% [95% CI, 2–12%; I^2 = 74.9%]; four studies,[6–8,18] *n* = 551), microscopic colitis (6% [95% CI, 3–10%; I^2 = 71.2%]; six studies,[5–9,18] *n* = 734), disaccharide intolerance (5% [95% CI, 3–8%; I^2 = 45.6%]; six studies,[5–8,10,18] *n* = 698), and inflammatory bowel disease (IBD) (2% [95% CI, 0–4%; I^2 = 61.1%]; four studies,[6,8,9,18] *n* = 588), each with a prevalence of 2–6%. Other causes of NRCD with their pooled prevalence are outlined in Table 3.

Discussion

The results of the present systematic review suggest that approximately one in five patients with CeD would be unresponsive to GFD and will likely be classified as NRCD. The most common cause of NRCD is inadvertent exposure to gluten, followed by functional gastrointestinal disorders and RCD type 1.

One of the desired hallmarks of treatment of CeD with GFD is not only resolution of symptoms but also attainment of nutritional deficiencies and abatement of immune response related to gliadin peptides as reflected by normalization of serological tests and healing of intestinal mucosa.[2] Continued intestinal and extraintestinal manifestations of CeD because of partial or complete lack of response to GFD may lead to lower quality of life.[19–21] Ongoing symptoms among patients with NRCD lead to not only continued suffering but also direct healthcare costs associated with additional healthcare visits, testing, and treatment, further adding to the already high healthcare utilization by patients with CeD.[22] NRCD might also be associated with indirect costs such as decreased work productivity, absenteeism, and use of non-prescription or over-the-counter medications. Finally, given persistent intestinal inflammation and malabsorption, certain complications of CeD such as anemia and loss of bone mineral density may persist in patients with NRCD that would otherwise have improved in patients who respond adequately to GFD.[23,24] Despite alteration in total cholesterol, high-density lipoprotein, fasting glycemia, and body mass index, the overall effect

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of GFD on cardiovascular risk in patients with CeD remains unclear at present, but they are of clinical importance.[25] Studies assessing direct and indirect healthcare costs and metabolic consequences associated with NRCD are thus required.

Non-adherence to GFD is one of the most frequent challenges faced by patients with CeD, with inadvertent gluten intake being more common than intentional non-adherence.[26] Studies have demonstrated a high prevalence of gluten contamination among available gluten-free food options.[27] A recent meta-analysis including 24 studies across 11 countries reported the pooled prevalence of gluten contamination (> 20 ppm) in industrial and non-industrial food products to be 13.2% (95% CI, 10.8–15.7%) and 41.5% (95% CI, 16.6–66.4%), respectively.[28] Lack of awareness about the available gluten-free food options is another important contributing factor. In a study by Silvester *et al.* (n = 105), over 60% of participants with CeD did not suspect they may have consumed gluten until they experienced a reaction to it.[29] In addition to lack of gluten-free options or lack of awareness of the same, social factors can contribute to gluten intake—such as feeling of embarrassment in inquiring about gluten-free food options, being hesitant to unknowingly offending the host, and simply wanting to blend in with others.[29]

RCD was observed to be an important cause of NRCD in the present systematic review. RCD type II is known to have a poor prognosis, and about 50% of patients develop EATL.[30,31] Recent studies have shown that the monoclonal expansion of aberrant IELs seen in RCD type II is an early sign of EATL, which leads to the more aggressive clinical course as compared with RCD type I.[31] However, it is still not clear if RCD type I can progress to type II. A study from UK[32] found that among patients with RCD who did not demonstrate these abnormalities at the time of diagnosis of RCD, 8 of 10 (80%) and 5 of 11 (45%) cases progressed to an aberrant phenotype and monoclonality, respectively, therefore suggesting a transition from RCD type I to RCD type II. They also observed a progressive increase in aberrant IELs (at a rate of 1.8% per month or 11% over 6 months) to above the diagnostic threshold for RCD type II, coinciding with the development of TCR clonality.[32] For making a diagnosis of RCD type I, all other causes of NRCD must be systematically ruled out; therefore, there is a need for a biomarker for differentiation of RCD from other causes of NRCD.

In the present systematic review, IBS and functional gastrointestinal disorders were also common causes of NRCD. These have been shown to be associated with CeD.[33] As compared with healthy controls, patients with IBS are more likely to possess the genetic predisposition (HLA-DQ2/DQ8) associated with the development of CeD.[34] In the setting of NRCD, functional gastrointestinal disorders must be diagnosed by exclusion, and their independent management is important. Similar to IBS, patients with CeD can have other associated disorders as well such as pancreatic insufficiency, SIBO, microscopic colitis, IBD, and lactose intolerance. Therefore, workup for other organic etiologies of NRCD is essential. Additionally, multiple studies have reported incorrect index diagnosis to be the cause of persistent symptoms in patients initially reported to have CeD.[7–10] The diagnostic flow algorithms proposed by many professional societies are already in place, and they should be followed in clinical practice.[4,13,35]

Hence, it is crucial to undertake specific measures in our community to improve the well-being of these patients with NRCD. First, we must reinforce adherence to well-accepted guidelines for making the diagnosis of CeD. Multiple studies have documented cases where patients referred for NRCD were later found to have an incorrect index diagnosis. This can result in a delay in treatment of the underlying disease. Second, patients with CeD should receive ongoing comprehensive counseling regarding GFD especially within the first year of diagnosis. Gluten-free products are also not readily available in stores/restaurants, are often more expensive, and are inadequately labeled, all of which hamper the strict adherence to the lifelong diet and predispose to dietary lapses.[36,37] As gluten is used extensively in the food industry, food labeling is essential for the identification of gluten-free foods, although many countries still lack legislation relating to the labeling of gluten in food products. Effective measures should be taken to combat the psychosocial impact of CeD and to break down the social barriers that may contribute to inadvertent gluten exposure. Additionally, a systematic workup should be followed when approaching a patient with NRCD. Lastly, there is a need for novel pharmacological approaches in management of CeD, and several promising drugs are already in development.[38,39]

Our study has many notable strengths, including a comprehensive search of literature, careful selection of relevant articles, and a rigorous appraisal of evidence. To our knowledge, this is the first meta-analysis to provide insights into the prevalence and etiologies of NRCD. However, the limitations of our review must be acknowledged. The available data on NRCD were limited to only two continents across the world. This underscores the need for more studies on prevalence of NRCD from other parts of the world specifically Asia and South America, where challenges in continuing a strict GFD might be higher or different from those in the USA and Western Europe. Additionally, some of the available data included tertiary care centers where patients had been referred, which falsely lead to overestimation of the prevalence of NRCD. Studies published in languages other than English were excluded. There was significant heterogeneity when we pooled data from these studies, but this was in part explained by characteristics of the study such as study population and duration of GFD.

In conclusion, one in five patients with CeD may have persistent signs and symptoms of CeD and hence qualify for the diagnosis of NRCD. While the most common cause of NRCD is inadvertent exposure to dietary gluten, it is important to pursue a comprehensive diagnostic workup to identify the underlying cause of NRCD.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting information.

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