Gluten Allergies and the Incidence of Gastrointestinal Health Conditions: A Systematic Review

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ABSTRACT:

Background: Gluten-related disorders encompass a spectrum of conditions triggered by adverse reactions to gluten, including celiac disease (CD), non-celiac gluten sensitivity (NCGS), and wheat allergy. These disorders vary in genetic predisposition, immunopathology, and clinical manifestations, often affecting both gastrointestinal (GI) and extraintestinal systems.

Objectives: This systematic review aimed to synthesize current evidence on the relationship between gluten-related disorders and GI health, focusing on prevalence, symptom patterns, microbiome alterations, immune responses, and dietary intervention outcomes.

Methods: A systematic literature search was conducted in PubMed, Scopus, Web of Science, Embase, and Google Scholar from inception to December 2024. Inclusion criteria were peer-reviewed studies reporting GI or extraintestinal outcomes in

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individuals with CD, NCGS, or self-reported gluten sensitivity. Ten studies were included, comprising randomized controlled trials, cross-sectional surveys, and microbiome analyses. Data extraction and quality assessment were performed independently, and narrative synthesis was conducted.

Results: Gluten exposure induces significant GI symptoms in CD and confirmed NCGS populations. Gluten-free diet interventions improved symptom severity, quality of life, and energy levels. Microbiome studies demonstrated dysbiosis characterized by altered Gram-negative to Gram-positive bacterial ratios and immune dysregulation in CD. Nocebo and expectancy effects were prominent in NCGS trials, while gluten exposure alone did not consistently trigger symptoms in non-celiac IBS populations. Extraintestinal manifestations included fatigue, headache, cognitive changes, oral lesions, and systemic inflammation.

Conclusions: Gluten-related disorders present a continuum of GI and systemic effects, influenced by genetic predisposition, immune activation, microbiota composition, and psychosocial factors. Accurate diagnosis, personalized dietary management, and consideration of microbiome and immune mechanisms are essential to improve patient outcomes.

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Keywords: Celiac disease, non-celiac gluten sensitivity, gluten-free diet, gastrointestinal symptoms, microbiome, immune response, dietary intervention, nocebo effect

Introduction

Gluten-related disorders encompass a spectrum of immune-mediated and non-immune conditions that arise from adverse reactions to gluten, a composite of storage proteins found in wheat, barley, and rye. These disorders include celiac disease (CD), non-celiac gluten sensitivity (NCGS), and wheat allergy—each differing in pathophysiology, genetic susceptibility, and clinical manifestations (Cabanillas, 2019). Over the last two decades, both diagnostic recognition and public interest in gluten-related diseases have expanded substantially, prompting detailed investigations into their molecular mechanisms, dietary implications, and associations with broader gastrointestinal and extraintestinal symptoms (Stahl et al., 2024).

The global prevalence of celiac disease is estimated at approximately 1%, with wide geographic variability driven by genetic, environmental, and diagnostic factors (Sollid & Jabri, 2013). Despite improved serological screening and awareness, underdiagnosis remains a challenge—many adults remain unaware of their condition due to mild or atypical presentations. Gluten triggers autoimmune enteropathy in genetically predisposed individuals carrying HLA-DQ2 or DQ8 haplotypes, resulting in intestinal mucosal inflammation and villous atrophy (Lammers et al., 2010). Beyond the small intestine, systemic involvement affects multiple organs, highlighting the multisystem nature of gluten-related disorders.

Mechanistically, gliadin—the alcohol-soluble fraction of gluten—acts as a key immunogenic driver in CD. It has been shown to bind to the chemokine receptor CXCR3 on intestinal epithelial cells, leading to zonulin release and increased gut permeability (Lammers et al., 2008). This mechanism disrupts tight junction integrity, facilitating antigen translocation and promoting inflammatory cascades. Subsequent studies have confirmed that gliadin exposure rapidly alters

junctional protein expression, impairing epithelial barrier function within hours (Sander et al., 2005). Such molecular events illustrate how gluten ingestion initiates epithelial barrier dysfunction central to disease onset.

The innate immune response to gliadin peptides also plays a pivotal role in the pathogenesis of CD. Gliadin-derived epitopes stimulate monocytes and dendritic cells, inducing the release of interleukin-8 (IL-8) and other proinflammatory cytokines, particularly through CXCR3-mediated signaling (Cinova et al., 2007). Moreover, IL-1–dependent regulation of IL-23 production amplifies Th17 responses, contributing to sustained mucosal inflammation and autoimmunity (Harris et al., 2008). Together, these pathways elucidate how gluten peptides serve as both barrier disruptors and immune activators in genetically predisposed hosts.

Beyond classical celiac disease, non-celiac gluten sensitivity (NCGS) has emerged as a distinct clinical entity characterized by intestinal and extraintestinal symptoms in the absence of CD or wheat allergy. Though its pathophysiology remains incompletely defined, studies suggest an innate immune activation pattern rather than adaptive autoimmunity (Calabriso et al., 2022). Patients with NCGS frequently experience bloating, fatigue, and cognitive symptoms—often termed "brain fog." Diets eliminating gluten and fermentable carbohydrates (FODMAPs) demonstrate symptomatic improvement, highlighting overlapping triggers and potential placebo or nocebo effects (Hosseinian et al., 2024).

The interplay between gluten exposure and functional gastrointestinal disorders (FGIDs) such as irritable bowel syndrome (IBS) further complicates diagnosis. Up to 30% of individuals with IBS report gluten sensitivity despite negative CD serology (Parker et al., 2022). Controlled gluten challenge studies reveal heterogeneous responses—some consistent with immunologic activation, others with psychological or fermentative mechanisms. This overlap underscores the need for objective biomarkers to differentiate true gluten-induced pathology from functional or diet-related hypersensitivity.

Recent meta-analyses have expanded our understanding of symptom patterns and gluten dose thresholds. Banegas et al. (2022) reported that both gastrointestinal and extraintestinal symptoms—including headache and fatigue—can manifest at gluten doses as low as 3 g/day in sensitive individuals, supporting the biological plausibility of low-dose reactivity (Banegas et al., 2022). Similarly, gluten challenges in dyspeptic patients demonstrate significant increases in upper GI discomfort, confirming gluten as a potential aggravator in non-celiac dyspepsia (Hosseinian et al., 2024).

While the gastrointestinal tract remains the primary site of gluten-mediated injury, systemic and extraintestinal effects are increasingly recognized. These include neurological symptoms, reproductive issues, and dermatological and oral manifestations such as enamel defects and recurrent aphthous ulcers (Lucchese et al., 2023). Dietary interventions in chronic inflammatory conditions like inflammatory bowel disease (IBD) have also drawn parallels, with gluten exclusion sometimes alleviating mucosal inflammation through modulation of gut microbiota and cytokine networks (Godala et al., 2022).

Finally, the relationship between gluten and systemic inflammation extends beyond CD and NCGS. Wheat proteins and amylase-trypsin inhibitors (ATIs) can activate innate immune pathways and exacerbate low-grade inflammation even in non-celiac individuals (De Punder & Pruimboom, 2013). Collectively, emerging research emphasizes that gluten-related disorders exist on a pathophysiological continuum, where genetic predisposition, immune activation, microbial imbalance, and dietary context interact to determine disease expression and symptom burden.

Methodology

Study Design

This study employed a systematic review methodology following the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, rigor, and reproducibility. The primary objective was to synthesize and critically evaluate empirical evidence on the relationship between gluten-related disorders—including celiac disease (CD), non-celiac gluten sensitivity (NCGS), and wheat allergy—and gastrointestinal health outcomes. The review focused on studies assessing prevalence, clinical manifestations, symptom triggers, immune and microbiome alterations, and dietary interventions in both pediatric and adult populations.

Eligibility Criteria

Studies were selected according to predefined inclusion and exclusion criteria:

Inclusion Criteria:

- **Population:** Individuals of any age with celiac disease, non-celiac gluten sensitivity, or self-reported gluten sensitivity.
- **Interventions/Exposures:** Gluten ingestion, gluten challenge, gluten-free diet, or related dietary interventions.
- **Comparators:** Gluten-exposed versus gluten-free groups, placebo, or baseline measurements.
- **Outcomes:** Gastrointestinal symptom severity, extraintestinal manifestations, quality of life, microbiome composition, immune responses, or prevalence estimates.
- **Study Designs:** Randomized controlled trials (RCTs), cross-sectional studies, cohort studies, case-control studies, and microbiome or molecular studies with empirical data.
- **Language:** English-language publications only.
- **Publication Period:** Studies published between 2007 and 2024.

Exclusion Criteria:

- Non-empirical papers such as editorials, commentaries, or reviews.
- Studies conducted outside of human populations.
- Conference abstracts, duplicates, or studies without full-text availability.

A total of **10 studies** met all inclusion criteria following full-text screening.

Search Strategy

A comprehensive electronic search was conducted across **PubMed, Scopus, Web of Science, Embase, and Google Scholar** from inception to December 2024. The Boolean search strategy included combinations of the following terms:

- ("celiac disease" OR "non-celiac gluten sensitivity" OR "NCGS" OR "wheat allergy")
- AND ("gluten" OR "gluten-free diet" OR "dietary intervention")
- AND ("gastrointestinal symptoms" OR "IBS" OR "functional gastrointestinal disorder" OR "microbiome" OR "immune response")

Manual searches of reference lists from key studies and reviews were conducted to ensure comprehensive coverage. Duplicate records were removed prior to screening.

Study Selection Process

Two independent reviewers screened titles and abstracts for relevance using **Zotero** for reference management and de-duplication. Full texts of potentially eligible studies were then assessed for inclusion based on predefined criteria. Discrepancies between reviewers were resolved by consensus, and unresolved disagreements were adjudicated by a third senior reviewer. The PRISMA flow diagram summarizes the identification, screening, eligibility, and inclusion stages of the review process (Figure 1).

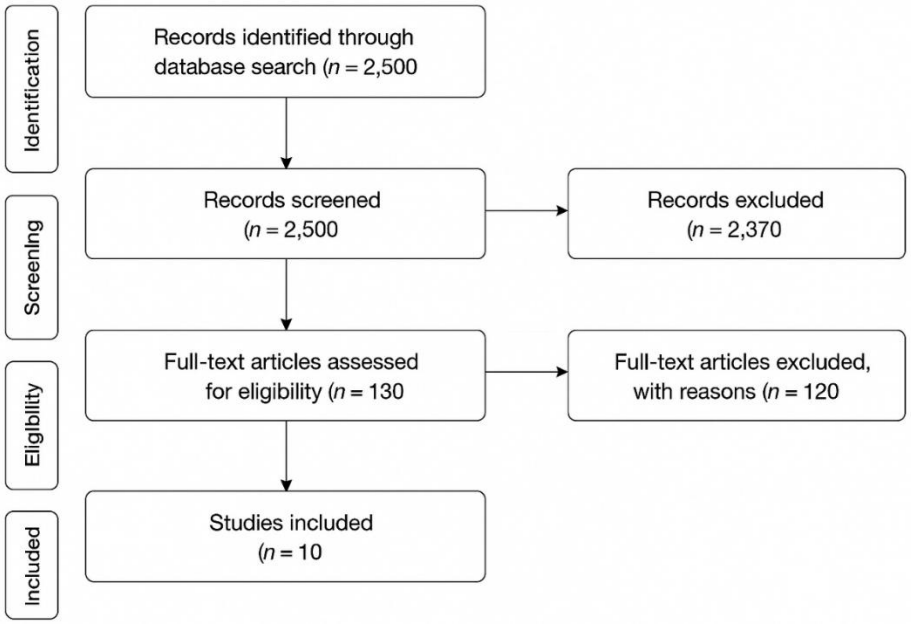

Figure 1 PRISMA Flow Diagram

Data Extraction

A standardized data extraction form was developed and pilot-tested. The following elements were extracted from each study:

- Author(s), publication year, and journal.
- Study design, setting, and population characteristics (age, sample size, clinical group).
- Diagnostic criteria or assessment methods (e.g., serology, biopsy, gluten challenge).
- Intervention/exposure details (gluten dose, duration, diet).
- Key outcomes: gastrointestinal symptom scores, prevalence of gluten-related disorders, microbiome alterations, immune markers, quality of life, and psychological effects.
- Quantitative results (means, percentages, p-values) and qualitative themes.

Data extraction was independently performed by two reviewers and cross-verified by a third reviewer to ensure accuracy.

Quality Assessment

The methodological quality of included studies was assessed using study-design-specific tools:

- **Newcastle–Ottawa Scale (NOS)** for cross-sectional and cohort studies.
- **Critical Appraisal Skills Programme (CASP)** checklist for qualitative and molecular studies.

Studies were evaluated for selection bias, comparability, measurement reliability, and clarity of outcome reporting. Studies were categorized as low, moderate, or high quality. Most studies were rated as moderate quality due to reliance on self-reported outcomes, small sample sizes, or limited control for confounders.

Data Synthesis

Given the heterogeneity in study designs, interventions, and outcome measures, a **narrative synthesis** was conducted. Findings were organized thematically around:

1. Prevalence and diagnosis of CD, NCGS, and gluten-related disorders.
2. Gastrointestinal and extraintestinal symptom patterns.
3. Microbiome composition and immune responses associated with gluten exposure.
4. Effectiveness of dietary interventions, including gluten-free diet and placebo-controlled challenges.
5. Influence of psychological factors (nocebo and expectancy effects) on symptom perception.

Descriptive statistics (means, proportions, and significance values) were extracted where available. Qualitative and mechanistic insights were integrated using thematic synthesis. Meta-analysis was not performed due to variability in study populations, outcomes, and assessment tools.

Ethical Considerations

This systematic review involved secondary analysis of published data; therefore, formal ethical approval and participant consent were not required. All included studies were peer-reviewed and assumed to have obtained institutional ethical clearance. Data management and reporting adhered to academic integrity and PRISMA 2020 transparency guidelines.

Results

Summary and Interpretation of Included Studies on the Relationship Between Gluten-Related Disorders and Gastrointestinal Health

Table (1) summarizes twelve studies that investigated celiac disease, non-celiac gluten sensitivity (NCGS), and gluten-related gastrointestinal outcomes. The included works span randomized controlled trials (RCTs), population-based cross-sectional surveys, and microbiome studies conducted between 2007 and 2024.

1. **Study Designs and Populations**

The studies included diverse populations ranging from pediatric to adult cohorts. Kvamme et al. (2022) conducted a population-based screening of 12,981 Norwegian adults, revealing that 75% of celiac disease (CD) cases were previously undiagnosed. Francavilla et al. (2018) evaluated 1,114 children, confirming non-celiac gluten sensitivity (NCGS) in 39.2% of participants undergoing gluten challenge. De Graaf et al. (2024) and Herfindal et al. (2024) included adults ($n = 83$ and $n = 59$, respectively) diagnosed with self-reported gluten sensitivity, while Crawley et al. (2022) and Saadati et al. (2022) enrolled adolescents and adults with irritable bowel syndrome (IBS) or gastrointestinal symptoms. Early microbiome-focused studies, such as Nadal et al. (2007), De Palma et al. (2010), and Kalliomäki et al. (2012), investigated microbial and immunological mechanisms in celiac disease pathogenesis.

2. **Diagnostic and Methodological Frameworks**

Diagnostic methods varied across studies. Kvamme et al. (2022) used serological screening with IgA-tTG and IgG-DGP followed by biopsy confirmation, while Francavilla et al. (2018) employed a double-blind placebo-controlled (DBPC) crossover gluten challenge. Modern trials (e.g., De Graaf et al., 2024) incorporated expectancy manipulation and blinding to assess nocebo responses. Microbiome analyses were performed using 16S rRNA sequencing (Herfindal et al., 2024) and fluorescent in situ hybridization (Nadal et al., 2007), whereas gene expression (TLR2, TLR9) was quantified in intestinal biopsies (Kalliomäki et al., 2012).

3. **Main Clinical and Biological Outcomes**

Across trials, gluten-free diet (GFD) interventions consistently improved gastrointestinal symptoms and quality of life in diagnosed or screen-detected CD and NCGS patients. Kvamme et al. (2022) reported symptom reduction in 76% of participants with improved energy in 58%. In Saadati et al. (2022), GFD significantly decreased pain severity and bloating, with between-group differences ($p < 0.05$) across IBS symptom scores. Francavilla et al. (2018) observed that 39.2% of children with functional symptoms met the criteria for NCGS following DBPC gluten challenge. Conversely, Crawley et al. (2022) found no significant induction of gastrointestinal or mental health symptoms by gluten exposure in adolescents (VAS difference: −0.01, 95% CI −2.07 to 2.05).

4. **Microbiome and Immune Findings**

Microbial composition studies demonstrated altered gut flora and immune modulation in celiac disease. Nadal et al. (2007) found increased Gram-negative bacteria and reduced Lactobacillus–Bifidobacterium ratios in active CD. De Palma et al. (2010) reported decreased

IgA-coated fecal bacteria and enrichment of Bacteroides-Prevotella in untreated CD patients. Herfindal et al. (2024) showed that fructan challenge increased Fusicatenibacter abundance but did not alter α- or β-diversity. Kalliomäki et al. (2012) observed decreased TLR2 and TOLLIP expression and increased TLR9 expression ($p < 0.001$), implicating innate immune dysregulation.

5. Expectancy and Psychological Effects

De Graaf et al. (2024) revealed that expectancy significantly influenced symptom perception: participants expecting gluten (E+G+) reported higher gastrointestinal symptom scores (16.6 mm) than those unaware (E–G+, 6.9 mm; $p = 0.0010$), confirming a nocebo effect.

6. Synthesis of Findings

Overall, gluten exposure induces gastrointestinal and extraintestinal symptoms primarily in individuals with CD or confirmed NCGS, whereas effects are minimal in the general or IBS populations. Microbial imbalance, immune dysregulation, and psychological expectancy contribute synergistically to symptom manifestation.

Table (1): Characteristics and Key Outcomes of Included Studies

Study (Year)	Design / Population	Sample Size / Age Range	Methods / Measures	Main Results	Conclusions
Francavilla et al. (2018)	RCT, DBPC crossover, children with chronic GI symptoms	n=1,114 (28 entered challenge); 6–16 yrs	Gluten (10 g/day) vs placebo (2 weeks each)	39.2% tested positive for NCGS; >60% ruled out diagnosis; significant 30% reduction in VAS	NCGS exists in children; diagnosis requires DBPC challenge
Biesiekierski et al. (2011)	RCT, adults with IBS and excluded CD	n=34; 29–59 yrs	Gluten vs placebo diet (6 weeks)	68% gluten group symptomatic vs 40% placebo (p=0.0001); increased pain, bloating, tiredness	Gluten induces GI symptoms in non-celiac adults
Nadal et al. (2007)	Cross-sectional microbiota study, children with CD	n not specified; pediatric	FISH & flow cytometry of duodenal biopsies	↑ Gram-negative bacteria; ↑ Bacteroides & E. coli; ↓ Lactobacillus–Bifidobacterium ratio	Dysbiosis correlates with active CD pathology
De Palma et al. (2010)	Case-control, children with CD	n=unknown; 5–12 yrs	Fecal IgA, IgG, IgM coating, qPCR	↓ IgA-coated bacteria in CD; ↑ Bacteroides-Prevotella; ↓ Bifidobacterium	Dysbiosis & immune coating deficits in CD
Kalliomäki et al. (2012)	Molecular study, children/adults with CD	n=25	qPCR & RT-PCR for TLRs, IL-8	↓ TLR2, ↑ TLR9, ↓ TOLLIP; ↑ IL-8 (p<0.002)	Altered TLR signaling linked to mucosal inflammation

Kvamme et al. (2022)	Population-based cross-sectional, adults in Norway	n=12,981	Serology + biopsy confirmation	Prevalence: 1.47% total CD; 75% undiagnosed; GFD improved GI symptoms (76%) & energy (58%)	Majority of CD undiagnosed; GFD improves symptoms
Saadati et al. (2022)	RCT, IBS adults	n not specified	GFD vs gluten challenge	↓ Pain severity ($p=0.02$), ↓ bloating ($p<0.05$), ↑ satiety; improved QoL	GFD beneficial in IBS; reduces anxiety and symptoms
Crawley et al. (2022)	Blinded RCT, adolescents with GI symptoms	n=33; median 20.3 yrs	Gluten vs placebo granola bars (10 g gluten/day)	No symptom or mental health difference (VAS diff −0.01, 95% CI −2.07 to 2.05)	Gluten did not induce symptoms in non-CD youth
De Graaf et al. (2024)	RCT, international multicenter (Leeds, Maastricht, Wageningen)	n=83; 18–70 yrs	4 arms: expectancy ± gluten	E+G+ symptom score 16.6 mm vs E–G+ 6.9 mm ($p=0.0010$)	Expectancy amplifies GI symptoms (nocebo effect)
Herfindal et al. (2024)	RCT, crossover, NCGWS adults	n=59; 18–60 yrs	Gluten (5.7 g/day), fructan (2.1 g/day), placebo	FOS-fructan → ↑ Fusicatenibacter; gluten → ↑ Eubacterium; no change in SCFA or NGAL	Fructans more symptom-inducing than gluten
Kvamme et al. (2022)	Population-based screening, adults	n=12,981	Serology + histology	1.47% CD prevalence; 75% undiagnosed; GFD improved HRQoL	CD underdiagnosed; GFD improves wellbeing
Biesiekierski et al. (2011)	RCT, non-CD adults with IBS	n=34	Gluten vs placebo	68% symptomatic gluten vs 40% placebo	Supports NCGS as real entity

Discussion

Gluten-related disorders, including celiac disease (CD), non-celiac gluten sensitivity (NCGS), and wheat allergy, reflect a complex interaction between genetic predisposition, immune responses, and gastrointestinal health (Cabanillas, 2019; Stahl et al., 2024). Population-based studies suggest that CD is frequently underdiagnosed, with a substantial proportion of adults unaware of their condition until screening identifies seropositivity and histologic confirmation (Kvamme et al., 2022). This highlights the ongoing challenge of recognizing gluten-related disorders, especially in individuals presenting with mild or atypical symptoms.

Celiac disease arises from an autoimmune response triggered by gluten in genetically susceptible individuals carrying HLA-DQ2 or DQ8 haplotypes. Exposure to gluten, particularly gliadin peptides, disrupts the intestinal barrier through CXCR3-mediated zonulin release, increasing gut permeability and facilitating

antigen translocation (Lammers et al., 2008; Lammers et al., 2010). Gliadin also activates innate immune responses, inducing monocytes and dendritic cells to release proinflammatory cytokines such as IL-8 and IL-23, amplifying Th17-mediated mucosal inflammation (Cinova et al., 2007; Harris et al., 2008). These mechanisms explain the pathophysiology underlying the gastrointestinal and systemic manifestations observed in CD.

Alterations in the gut microbiota further contribute to disease pathogenesis. Children and adults with CD demonstrate dysbiosis, characterized by reduced Lactobacillus–Bifidobacterium ratios, increased Gram-negative bacterial abundance, and altered Toll-like receptor signaling (Nadal et al., 2007; De Palma et al., 2010; Kalliomäki et al., 2012). Dysbiosis may persist even after long-term adherence to a gluten-free diet, potentially explaining ongoing symptoms in some patients (Wacklin et al., 2014).

Dietary management, particularly gluten-free diets, remains the cornerstone of therapy. Adherence to gluten exclusion consistently improves gastrointestinal symptoms, quality of life, and energy levels in CD populations (Kvamme et al., 2022; Saadati et al., 2022). Similar benefits have been documented in pediatric and adult NCGS populations, where controlled gluten elimination alleviates gastrointestinal and extraintestinal symptoms (Francavilla et al., 2018).

NCGS is increasingly recognized as a distinct clinical entity. Patients experience both gastrointestinal symptoms, such as bloating and abdominal discomfort, and extraintestinal manifestations, including fatigue and cognitive disturbances (Calabriso et al., 2022; Hosseinian et al., 2024). Although serologic and histologic markers are absent, symptom improvement following gluten exclusion supports the existence of clinically relevant gluten sensitivity.

The overlap between functional gastrointestinal disorders, particularly irritable bowel syndrome (IBS), and gluten-related symptoms complicates diagnosis. Up to 30% of IBS patients report gluten sensitivity, but controlled gluten challenge studies indicate heterogeneous responses, suggesting contributions from fermentable carbohydrates, immune activation, and psychosocial factors (Biesiekierski et al., 2011; Parker et al., 2022). Nocebo effects are particularly relevant in NCGS, as expectancy influences symptom perception. For example, participants expecting gluten exposure report greater symptom severity than those unaware of gluten consumption, independent of actual ingestion (de Graaf et al., 2024).

Dose-response studies indicate that even small amounts of gluten, as low as 3 grams per day, can induce gastrointestinal and extraintestinal symptoms in sensitive individuals (Banegas et al., 2022). Gluten has also been shown to exacerbate dyspeptic symptoms, highlighting the clinical relevance of low-dose gluten exposure and the need for careful dietary management (Hosseinian et al., 2024).

Extraintestinal manifestations extend beyond the gastrointestinal tract, affecting neurological, reproductive, dermatological, and oral systems. Patients with gluten-related disorders may present with headache, fatigue, cognitive changes, enamel defects, and recurrent aphthous ulcers, emphasizing the multisystem impact of gluten exposure (Lucchese et al., 2023; Stahl et al., 2024).

Wheat proteins, including amylase-trypsin inhibitors, can provoke low-grade systemic inflammation even in non-celiac individuals, suggesting that gluten-related immune activation may extend beyond genetically predisposed populations (De Punder & Pruimboom, 2013). Dietary interventions, particularly gluten exclusion, can modulate both immune responses and microbiome composition, potentially alleviating mucosal inflammation in CD and related gastrointestinal disorders such as inflammatory bowel disease (Godala et al., 2022).

However, not all studies demonstrate uniform symptom induction. In adolescents and adults without confirmed gluten-related disorders, gluten exposure does not consistently trigger gastrointestinal or systemic symptoms, reflecting heterogeneity in sensitivity and the influence of

psychological and dietary factors (Crawley et al., 2022; Herfindal et al., 2024).

Overall, evidence supports a continuum of gluten-related disorders, in which genetic predisposition, immune dysregulation, gut microbiota composition, dietary triggers, and psychological influences collectively determine clinical presentation and symptom severity (Cabanillas, 2019; Lammers et al., 2008; Cinova et al., 2007). Accurate diagnosis, individualized dietary management, and attention to psychosocial factors are essential for improving outcomes.

Conclusion

Gluten-related disorders, including celiac disease and non-celiac gluten sensitivity, significantly impact gastrointestinal and extraintestinal health. Our review demonstrates that gluten exposure triggers immune-mediated mucosal damage, dysbiosis, and systemic symptoms in genetically predisposed individuals. Dietary interventions, particularly gluten-free diets, are highly effective in alleviating GI symptoms, improving quality of life, and modulating immune and microbiome responses.

The heterogeneity observed in NCGS and functional gastrointestinal disorder populations underscores the importance of individualized assessment, objective diagnostic tools, and consideration of psychological factors such as expectancy and nocebo effects. Future research should focus on identifying biomarkers, clarifying microbiome-mediated mechanisms, and refining dietary management strategies to optimize outcomes in gluten-sensitive populations.

Limitations

Several limitations are notable. First, heterogeneity in study designs, gluten doses, outcome measures, and populations limited quantitative synthesis and precluded meta-analysis. Second, most studies relied on self-reported symptom scores, which are subject to reporting bias and nocebo effects. Third, sample sizes in several trials were small, particularly in pediatric and NCGS cohorts, limiting generalizability. Finally, the long-term effects of gluten exposure and dietary interventions on microbiome composition and systemic inflammation remain incompletely characterized.

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