Non-coeliac gluten sensitivity

Jessica R Biesiekierski, Daisy Jonkers, Carolina Ciacci, Imran Aziz

Non-coeliac gluten sensitivity (NCGS) refers to individuals who report intestinal and extraintestinal symptoms related to the ingestion of gluten-based or wheat-based foods, in the absence of coeliac disease or wheat allergy. Gluten is found in multiple cereals, including wheat, rye, and barley, although the precise trigger of symptoms in NCGS remains unclear. Although approximately 10% of adults worldwide self-report gluten or wheat sensitivity, meta-analyses suggest that, during controlled challenge studies, 16–30% of these individuals have symptoms specifically triggered by gluten. However, methodological variability—including the presence of fermentable carbohydrates in challenge preparations—limits interpretation. Current evidence suggests that fermentable carbohydrates and nocebo effects contribute considerably to symptom generation in many cases. The substantial size of the gluten-free market raises questions about commercial and media influences on how NCGS is portrayed, and on the direction of related research. Definitive diagnosis of NCGS remains elusive due to the absence of biomarkers, significant overlap with disorders of gut–brain interaction, and methodological challenges in dietary evaluation. Until causative agents are identified and diagnostic tests developed, NCGS remains a diagnosis of exclusion, requiring careful systematic evaluation. Management approaches should balance dietary modification with recognition of psychological factors while ensuring nutritional adequacy. This Review critically examines current evidence regarding NCGS as a distinct entity, explores potential mechanisms, and provides practical guidance for assessment and management, while acknowledging major uncertainties in the field.

Published **Online**
October 22, 2025
https://doi.org/10.1016/S0140-6736(25)01533-8

School of Agriculture, Food and Ecosystem Sciences, Faculty of Science, The University of Melbourne, Melbourne, VIC, Australia (J R Biesiekierski PhD); **Department of Gastroenterology-Hepatology, Nutrim Institute of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center, Maastricht, Netherlands** (Prof D Jonkers PhD); **Department of Medicine, Surgery and Dentistry, Scuola Medica Salernitana, University of Salerno, Salerno, Italy** (Prof C Ciacci MD); **Academic Department of Gastroenterology, Sheffield Teaching Hospitals, Sheffield, UK** (I Aziz MD); **Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield, UK** (I Aziz)

Correspondence to:
Assoc Prof Jessica R Biesiekierski, School of Agriculture, Food and Ecosystem Sciences, Faculty of Science, The University of Melbourne, Melbourne, VIC 3010, Australia
jessica.biesiekierski@unimelb.edu.au

Introduction

Non-coeliac gluten sensitivity (NCGS) remains a highly contested clinical entity, with uncertainty about its existence as a distinct condition. Although approximately 10% (range 4·3–14·9%) of the world's population self-report gluten or wheat sensitivity,[1] this number substantially overstates the true prevalence of clinically verified cases. Meta-analyses suggest that, in controlled challenge studies, 16–30% of individuals who self-report gluten sensitivity have symptoms triggered by gluten.[2,3] However, these estimates are based on studies with considerable methodological variability, limiting their interpretation. In the largest of the analyses,[2] a gluten-specific effect was observed in only three studies that adhered to predefined criteria; across all included studies, the pooled effect did not differ from placebo. Several trials used open-label designs or gluten preparations that included fermentable carbohydrates, making interpretation even more complex. Most reported symptoms appear to be attributable to other wheat components, particularly fermentable carbohydrates, or to nocebo effects.[4]

The substantial size of the global gluten-free diet market—projected to reach US$11·48 billion by 2029[5]—raises questions about potential commercial influences on scientific discourse and public health narratives.[6,7] The rapid expansion of the gluten-free diet market has paralleled increasing public concern about the health effects of gluten, creating a cycle in which consumer demand and market growth can reinforce each other.[8] This dynamic can subtly shape research priorities and can influence how narratives around NCGS are constructed.[9] Key clinical tools, such as the Salerno diagnostic criteria,[10] emerged from a meeting funded by a gluten-free food manufacturer, with authors transparently disclosing industry relationships. This intersection of commercial interests and clinical guidance highlights how health concerns and market opportunities can align, potentially shaping how NCGS is conceptualised.[6]

The emergence of NCGS as a modern clinical concept remains controversial. Claims about changes in wheat agriculture affecting protein composition have not been supported by evidence. Studies examining German winter wheat cultivars from 1891–2010 found no statistically significant alterations in protein composition or immunostimulatory potential.[11,12] Research indicates that wheat composition has remained largely unchanged, particularly in the past 20 years, despite the growing popularity of gluten-free diets. Gluten concentrations naturally vary by wheat variety and environmental factors such as rainfall, and wheat consumption in the USA has notably declined in the past century.[13]

Search strategy and selection criteria

We searched PubMed from database inception to Jan 31, 2025, for references using the search terms "non-celiac OR non-coeliac OR nonceliac OR noncoeliac", AND "gluten sensitivity OR wheat sensitivity" in the title or abstract. Relevant articles in English were retrieved and reviewed. Forward and backward citation checks were carried out on selected relevant papers. We prioritised randomised control trials and publications from the past 10 years, but we cited other references when relevant, including guideline or consensus publications. Additional publications were identified from the reference lists of articles, conference proceedings, Google Scholar, and by manual searches of gastroenterology journals. We did not focus on patients with coeliac disease or other gluten-related disorders (gluten ataxia, autism, or neurological symptoms).

NCGS is characterised by intestinal and extraintestinal symptoms related to gluten-containing foods, occurring in the absence of coeliac disease or wheat allergy. However, the diagnostic criteria and underlying mechanisms for this condition remain poorly understood. A comprehensive diagnostic procedure requires more than self-reporting, necessitating a systematic approach that includes clinical assessment of symptoms, evaluation of response to a gluten-free diet, and a controlled gluten challenge.[10] This Review critically evaluates the current evidence for NCGS as a distinct clinical entity by: (1) examining the evidence from controlled dietary challenge studies; (2) assessing the overlap with other conditions, particularly disorders of gut–brain interaction (DGBI); (3) discussing the role of psychological factors and nocebo effects; (4) evaluating proposed mechanistic pathways; and (5) providing evidence-based approaches for diagnosis and management in the context of uncertainties.

Definition

The concept of NCGS first emerged in the late 1970s in reports of patients with gastrointestinal symptoms attributed to gluten-based products, without evidence of coeliac disease, who improved on a gluten-free diet.[14,15] However, together with increasing attention from the general population, evidence began to spark academic attention and curiosity after the millennium.[16]

The terminology remains contested: although NCGS has been widely established in the medical literature, some experts suggest that non-coeliac wheat sensitivity might be more appropriate.[17,18] This suggestion reflects growing evidence that components of wheat beyond gluten might cause symptoms. Given the complexities in disentangling specific triggers, terms such as self-reported NCGS, non-coeliac wheat sensitivity, non-coeliac cereal sensitivity, or more broadly, patients who avoid wheat and/or gluten are sometimes used interchangeably in the literature.[17,19] For clarity, this Review uses the term NCGS, but acknowledges the sizeable uncertainty surrounding the precise mechanisms and triggers of wheat-related symptoms.

Epidemiology

Cross-sectional observational studies worldwide suggest that approximately 10% of the population (range 4·3–14·9%) self-report gluten or wheat sensitivity.[1] Notably, the number of people avoiding dietary gluten is about twice that of those diagnosed with coeliac disease or self-reported non-coeliac wheat sensitivity.[20] However, these prevalence estimates are likely inflated due to several factors. Most existing studies rely heavily on self-reporting rather than clinical verification, and many individuals adopt gluten-free diets for reasons unrelated to medical indications, such as perceived benefits for weight loss, athletic performance, reduced inflammation, enhanced energy, or general wellness.[21] Symptoms attributed to gluten ingestion might instead be triggered by fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs)—short-chain carbohydrates known to cause digestive symptoms in sensitive individuals—or by other wheat components.[22,23] A substantial overlap with irritable bowel syndrome (IBS) and other DGBI also exists.[24,25]

Approximately a third of high-income populations report adverse food reactions; however, less than 3% of self-reported food sensitivities are validated by objective testing.[26] In the context of gluten sensitivity, the number of clinically verified cases is substantially lower than self-reported estimates.[2,3] Methodological differences in challenge protocols—including FODMAP contamination, placebo effects, open-label challenges, and varying definitions—make interpretation more complex. Even in controlled trials, gluten-specific effects have generally been limited to a small subset of rigorous studies.[2] Consequently, the true prevalence of verified NCGS is likely considerably lower than self-reported rates.

Distinguishing NCGS from related conditions is essential for accurate diagnosis. Coeliac disease is an autoimmune disorder, affecting approximately 1% of the population, and is triggered by gluten ingestion in genetically susceptible individuals.[27] It is characterised by mild intestinal damage and can present with a wide range of symptoms. By contrast, wheat allergy is an IgE-mediated immune reaction affecting 0·1–1% of the population. This condition typically presents with immediate allergic responses, including respiratory, gastrointestinal, or cutaneous symptoms. Unlike coeliac disease and wheat allergy, a clearly defined pathological mechanism for NCGS, specific diagnostic tests, and consistent clinical presentation are absent. The substantial differences between these conditions highlight the complexity of wheat-related disorders and underscore the need for precise diagnostic approaches.

Evidence for NCGS as a distinct entity

The assessment of NCGS research requires acknowledging considerable methodological limitations that affect the interpretation of all reported findings. These include substantial heterogeneity in participant selection (with varying approaches to excluding coeliac disease), challenge protocols (with different gluten vehicles, doses, and durations), and outcome measurements (with inconsistent symptom assessment tools and thresholds for clinical significance). Such inconsistencies limit the comparability of studies and contribute to the conflicting findings regarding NCGS as a distinct clinical entity.

To explore how these methodological factors have shaped the evidence base, selected double-blind placebo-controlled trials investigating gluten reactivity in individuals with suspected NCGS are presented in the table. These studies were chosen to show the evolution of

research in this field, from early foundational work to high-quality trials with substantial methodological advances, illustrating the varied findings that continue to influence the classification of NCGS. A comprehensive assessment of all major double-blind, placebo-controlled trials is provided in appendix 1 (pp 1–6).

Three methodologically robust studies have been instrumental in shaping our current understanding of symptom triggers in self-reported NCGS. Biesiekierski and colleagues showed no gluten-specific effects when participants were maintained on a low-FODMAP diet,[22] suggesting that previously observed symptoms might be attributed to fermentable carbohydrates rather than gluten. Skodje and colleagues further strengthened this evidence in a rigorously designed trial showing that, compared with placebo, fructans (a type of FODMAP), not gluten, induced IBS symptoms.[23] de Graaf and colleagues used an innovative factorial design to show that symptom severity was predominantly determined by participants' expectations rather than actual gluten content, providing the strongest evidence to date for psychological mechanisms in symptom generation.[4] Collectively, these studies challenge the premise of NCGS as a distinct entity defined by gluten-specific biological reactivity. Nonetheless, they remain individual investigations and have not yet been independently replicated. Additionally, the fructan used in the trial done by Skodje and colleagues was derived from chicory root rather than a gluten-containing cereal and was administered at a modest dose, which might limit the generalisability.[23]

See Online for appendix 1

A comprehensive scoping review by An and colleagues systematically evaluated evidence from 16 randomised controlled trials on proposed molecular triggers in NCGS.[28] The analysis revealed that only gluten and FODMAPs (specifically fructans) have been empirically investigated in controlled trials in humans. In studies examining gluten, only 50% showed statistically significant gluten-specific effects, with considerable methodological heterogeneity undermining definitive conclusions.[28] Further supporting this pattern, Iven and colleagues found that although participants with NCGS had increased fatigue and gastrointestinal symptoms compared with healthy controls during both acute and sub-acute gluten challenges, these responses were not gluten specific. Notably, more than half of participants

	Study design	Primary outcome	Evidence quality	Key finding	Importance to field
de Graaf (2024)[4]	DBPC parallel, randomised	Gastrointestinal symptom severity on VAS	High	Increased symptom scores in those expecting gluten, regardless of actual content (p<0·001)	Landmark study showing that expectancy effects are more influential than actual gluten content; strong evidence for nocebo mechanisms
Cooper (1980)[15]	DBPC crossover	Gastrointestinal symptom response after gluten challenge	Low	Significant worsening of intestinal symptoms with gluten (p<0·01)	First clinical report identifying gluten sensitivity without coeliac disease; historical foundation
Biesiekierski (2013)[22]	DBPC crossover, randomised	Change in overall symptom score	High	No gluten-specific symptom response; all groups similarly increased symptoms *vs* low-FODMAP run-in (p<0·0001)	Highlighted nocebo effects and suggested that FODMAPs, not gluten, might trigger symptoms in suspected NCGS
Skodje (2018)[23]	DBPC crossover, randomised	IBS-symptom severity scale score during challenges	High	Fructans, not gluten, increased IBS symptoms *vs* placebo (p=0·04)	First controlled trial directly comparing gluten and fructans, verifying FODMAP sensitivity as likely mechanism
Peters (2014)[36]	DBPC crossover, randomised	State depression scores	High	Significant increase in depression scores with gluten *vs* placebo (p=0·02)	First study to show extraintestinal psychological effects of gluten
Zanini (2015)[51]	DBPC crossover, randomised	Ability to correctly identify gluten flour	Moderate	Only 34% of participants correctly identified gluten flour; 49% incorrectly identified gluten-free flour as containing gluten	Showed poor reliability of self-reported gluten sensitivity
Biesiekierski (2011)[75]	DBPC parallel, randomised	Proportion with inadequately controlled symptoms	High	68% of participants in the gluten group reported inadequately controlled symptoms *vs* 40% with placebo (p=0·0001)	First randomised controlled trial showing gluten-specific symptom induction; established NCGS as potential clinical entity
Di Sabatino (2015)[78]	DBPC crossover, randomised	Change in overall symptom scores	High	Significant increase in overall symptoms with gluten *vs* placebo (p=0·034), but only three of 59 patients showed gluten sensitivity	Highlighted heterogeneity of NCGS population with only a small number showing clear gluten sensitivity
Francavilla (2018)[129]	DBPC crossover, randomised	Decrease in global VAS score	High	Significant increase in IBS symptom score with gluten *vs* placebo in 11 (39%) of 28 children with suspected NCGS	First paediatric DBPC study showing existence of NCGS in children

For complete methodological details and the full list of DBPC studies, see appendix 1 (pp 1–6). Evidence quality rating was based on methodological criteria, including adequate sample size, appropriate randomisation and blinding procedures, handling of dropout rates, appropriateness of controls and washout periods, clarity of predefined endpoints, and appropriate statistical analysis. DBPC=double-blind, placebo-controlled. FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. IBS=irritable bowel syndrome. NCGS=non-coeliac gluten sensitivity. VAS=visual analogue scale.

Table: **Double-blind, placebo-controlled dietary re-challenge studies investigating gluten reactivity in self-reported NCGS**

incorrectly attributed symptoms to gluten during placebo administration, reinforcing the powerful role of expectancy effects.[29]

Whether NCGS represents a discrete condition or a subset of patients with IBS and specific dietary triggers remains unclear. The high nocebo response rates[4] and frequent coexistence of other food intolerances[30] suggest that altered visceral sensitivity and psychological factors play important roles, similar to other DGBI.

The substantial overlap between NCGS and DGBI presents a dilemma in establishing NCGS as a distinct entity. Between 20% and 80% of individuals with suspected NCGS meet the diagnostic criteria for IBS,[24,25] and many improve on low-FODMAP diets independent of gluten content.[22,31,32] This overlap extends beyond gastrointestinal symptoms to include various extraintestinal manifestations commonly seen in DGBI, including fibromyalgia,[33] chronic fatigue,[34] cognitive symptoms (so-called foggy mind),[35] and psychiatric manifestations, such as depression.[36] Additionally, associations have been reported with conditions such as dermatitis herpetiformis[37] and various neurological manifestations.[38] However, the causal relationship between NCGS and these conditions remains unclear. Many symptoms also overlap with those of IBS[39] and other DGBI, generating difficulty in establishing whether they represent distinct manifestations of NCGS or reflect common underlying mechanisms of gut–brain interaction. This extensive symptom overlap necessitates comprehensive diagnostic evaluation that considers both gastrointestinal and extraintestinal manifestations while accounting for the considerable role of dietary triggers and psychological factors.

Clinical features

Demographic and presentation patterns

The typical phenotype of NCGS is most observed in individuals with a mean age of 38 years, and studies report that 72–84% of cases are in women. Most cases are initially self-diagnosed or identified through non-traditional health-care pathways.[40] Clinical presentation to physicians typically occurs to: (1) obtain systematic evaluation and validation of self-reported symptoms,[41] (2) exclude coeliac disease and wheat allergy,[10] and (3) address persistent symptoms despite dietary modification, which can indicate alternative conditions such as FODMAP sensitivity[22,23] or other DGBI.[24,42]

Symptoms generally develop within 2–6 h[43] after gluten or wheat exposure, although onset can sometimes extend to several days (figure 1).[41] The symptom pattern includes many gastrointestinal and extraintestinal manifestations, with considerable individual variation in severity and range. Common gastrointestinal symptoms include bloating (72–87%), abdominal pain and discomfort (55–83%), diarrhoea (16–60%), constipation (18–50%), nausea (9–44%), aerophagia (36%), reflux (32%), altered bowel habit (27%), and aphthous stomatitis (31%).[40,41] These intestinal manifestations significantly impact quality of life, with several studies showing that the severity of gastrointestinal symptoms correlates directly with reduced quality-of-life scores and increased psychological distress.[44]

Extraintestinal manifestations are frequently reported,[40,41,45] and also contribute substantially to quality-of-life impairment.[30,46,47] These commonly include headaches (20–54%),[48–50] fatigue (23–64%),[23,25] cognitive difficulties (so-called foggy mind; 10–42%),[40,41] and musculoskeletal pain (5–31%).[40,41] Iven and colleagues found that individuals with NCGS show distinct psychological characteristics at baseline, including a higher negative affect and a lower positive affect than healthy controls, suggesting that underlying psychological differences can contribute to symptom experience, independent of gluten exposure.[29] Depression and anxiety have been consistently reported in multiple studies;[36,41] however, whether these reflect direct effects of gluten exposure or psychological responses to chronic symptoms remains unclear.

NCGS has also been associated with other organic conditions, although causative relationships remain to be established. These conditions include autoimmune disorders, particularly Hashimoto's thyroiditis,[52] dermatological conditions including dermatitis herpetiformis-like skin lesions and psoriasis, rheumatological diseases,[53] and various neurological manifestations.[48] Nutritional assessments indicate that individuals with NCGS are more likely to have nutritional deficiencies and decreased bone mineral density compared with the general population, although these alterations are typically less severe than those in untreated coeliac disease.[19,24,54,55]

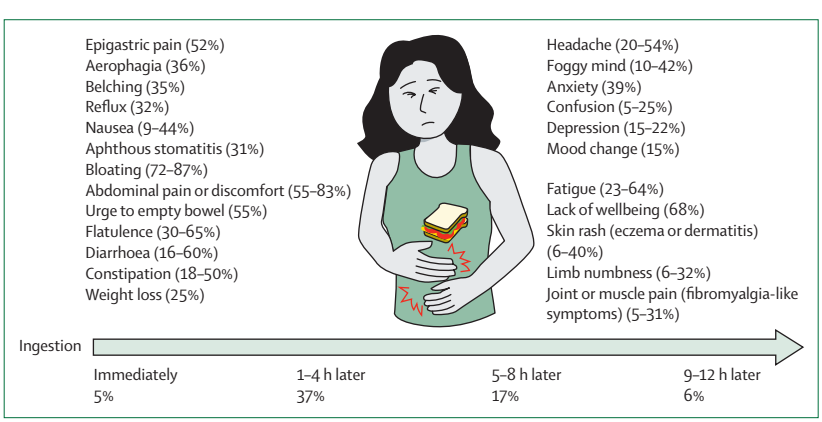

Figure 1: **Symptoms and onset times**
Data from questionnaires completed by individuals with self-reported non-coeliac gluten sensitivity, according to multiple reports: Aziz and colleagues[24] (UK n=1002), Volta and colleagues[25] (Italy n=486), Biesiekierski and colleagues[40] (Australia n=147), and de Graaf and colleagues[4] (prescreening data from the UK and the Netherlands n=301).

Nutritional considerations and dietary behaviour

Individuals with self-reported NCGS avoid not only gluten, but also a range of other foods, including fruits, vegetables, dairy, and spices, suggesting that their perceived sensitivities extend beyond gluten alone.[56]

Many do not adequately compensate nutritionally when eliminating gluten-containing products, often adopting imbalanced substitution patterns, rather than incorporating nutritionally equivalent alternatives.[44] This pattern mirrors broader dietary behaviour in IBS, in which more than 80% of individuals report that food either causes or aggravates their symptoms, with gluten-based products frequently cited by approximately one in four patients.[30] Without proper medical guidance, patients might progressively eliminate additional food groups to identify triggers, potentially leading to unnecessarily restrictive diets and nutritional deficiencies. This highlights the importance of systematic dietary assessment and professional guidance to maintain nutritional adequacy while effectively managing symptoms. This complex clinical presentation, substantially overlapping with DGBI and multiple dietary sensitivities, necessitates a systematic diagnostic approach that can effectively differentiate NCGS from other conditions, while also accounting for potential nocebo effects.

Screening, assessment, and diagnosis

A systematic diagnostic approach for suspected NCGS requires a structured three-phase process (figure 2), beginning with comprehensive initial screening to document symptom patterns and identify risk factors. The second phase focuses on the exclusion of alternative diagnoses, particularly coeliac disease and wheat allergy, which can present with similar symptoms, but require different management approaches. The final phase involves controlled dietary evaluation with elimination and challenge protocols, and remains the cornerstone of NCGS diagnosis in the absence of specific biomarkers. This systematic approach helps differentiate true gluten or wheat sensitivity from other conditions, while accounting for the major role of nocebo effects in symptom generation.

Diagnostic approach and differential considerations

In phase 1 of the diagnostic algorithm (figure 2), initial evaluation requires a detailed clinical history, including symptom patterns, dietary habits, and response to gluten exposure. This phase should include screening for alarm features and assessment of nutritional intake and dietary avoidance patterns. The psychological impact of symptoms should be considered, including the potential for fear-based food avoidance resembling avoidant/restrictive food intake disorder,[57] particularly given the significant role nocebo effects play in symptom generation.[4]

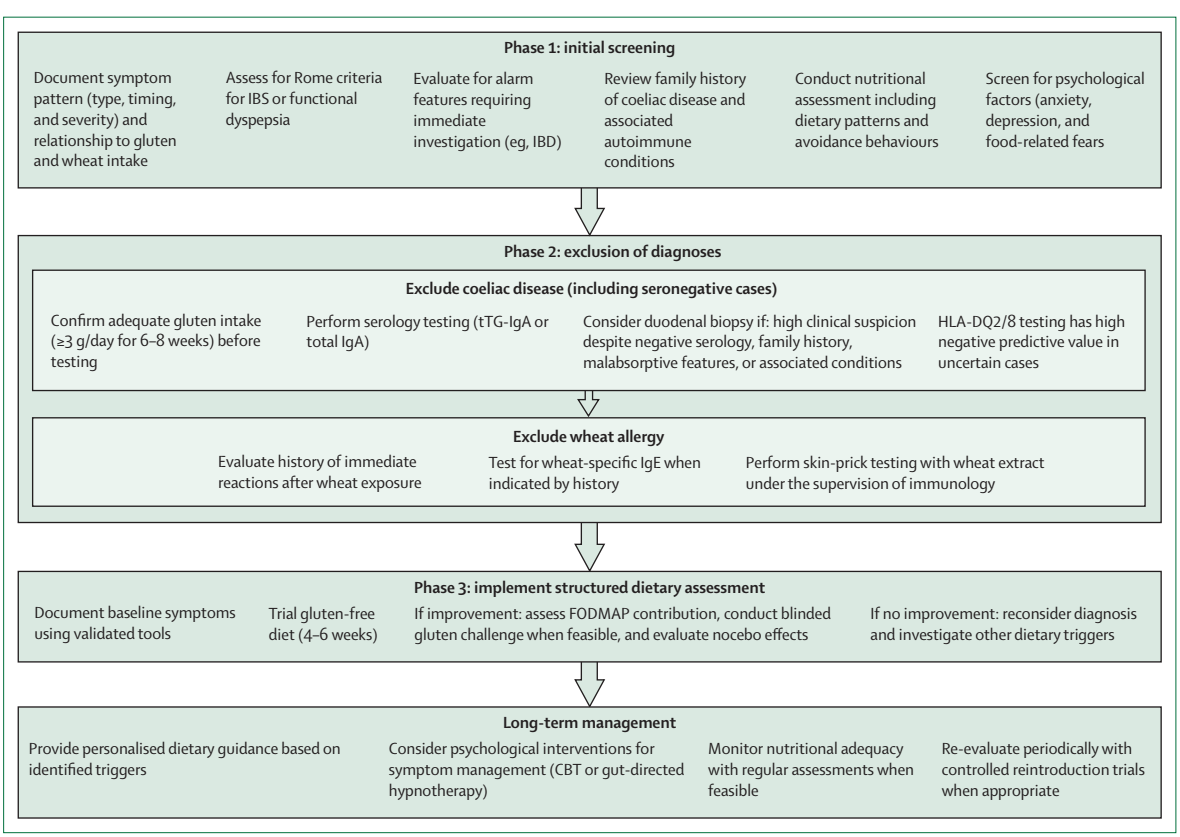

Figure 2: **Three-phase diagnostic pathway**
IBS=irritable bowel syndrome. IBD=inflammatory bowel disease. tTG=tissue transglutaminase. FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. CBT=cognitive behavioural therapy.

The next step is exclusion of alternative diagnoses, as outlined in phase 2 (figure 2). IgE-mediated wheat allergy, although rare in adults (0·8%),[58] requires exclusion with specific IgE testing and supervised oral challenges when indicated.[59] Clinical manifestations differ from NCGS and are characterised by immediate reactions (within minutes to hours) and vary by exposure route: urticaria with skin contact, rhinitis or occupational asthma with inhalation, and classic allergic manifestations or exercise-induced anaphylaxis with ingestion.[60,61]

Coeliac disease remains the primary differential diagnosis, requiring exclusion through serological testing (tissue transglutaminase or endomysial antibodies)[62] with a tissue transglutaminase IgA sensitivity of 81–84% and a specificity of 96–99%.[63] Maintaining adequate gluten intake (3–6 g/day for 6–8 weeks) before testing is essential.[64] The gold standard diagnosis requires histological verification of duodenal villous atrophy,[65–67] although some guidelines no longer require a biopsy sample to be taken in select scenarios with strongly positive coeliac serology.[68] Seronegative coeliac disease occurs rarely (2–3% of coeliac cases),[67] but poses unique diagnostic challenges, necessitating adequate gluten challenge and a biopsy done in suspicious cases.

Inflammatory bowel disease, although rare in adults (1·5%), should be considered in patients presenting with alarm features.[69] Although 4·9% of individuals with inflammatory bowel disease report NCGS,[70] they have higher rates of severe or stricturing Crohn's disease than individuals without NCGS.[69] Many patients with inflammatory bowel disease report IBS-like symptoms resembling NCGS and identify wheat as a symptom trigger.[71,72]

The substantial overlap between NCGS and DGBI represents the most frequent association encountered during diagnostic evaluation. Population-based studies show a significant association between NCGS and both IBS and functional dyspepsia. Data from the UK showed a higher prevalence of IBS in patients with NCGS than in those without (20% *vs* 3·9%, respectively; odds ratio [OR] 6·23, 95% CI 3·59–10·8),[24] with similar associations found in Australian cohorts (OR 3·55, 95% CI 2·71–4·65).[42] Functional dyspepsia is also more prevalent in patients with NCGS than those without (31·3% *vs* 13·6%, respectively; OR 1·48, 95% CI 1·13–1·94).[42] This consistent overlap, combined with evidence that many patients improve on low-FODMAP diets independent of gluten content,[22] has led some experts to propose that gluten or wheat sensitivity might represent one of several dietary triggers in patients susceptible to DGBI, rather than a distinct condition.

Role of nocebo effects

The nocebo effect appears to play a substantial role in symptom generation in patients with suspected NCGS. In a landmark study, de Graaf and colleagues showed that symptom severity was predominantly determined by whether participants expected to receive gluten, rather than actual gluten content.[4] Evidence from Biesiekierski and colleagues also supported psychological mechanisms, finding statistically significant order effects in their crossover trial—participants reported more symptoms during their first treatment period regardless of whether they received gluten or placebo.[22] This powerful expectancy effect helps explain why only 16% of patients with suspected NCGS show specific gluten reactivity in double-blind placebo-controlled challenges, while nocebo responses are substantial—averaging 40% in systematic reviews[73] and reaching as high as 56% in other studies.[29] Importantly, these findings do not invalidate patients' symptoms, but rather highlight the complex bidirectional interactions between the brain and gut that contribute to symptom generation, perception, and reporting. Understanding these brain–gut interactions is crucial for accurate diagnosis, patient education, and development of effective management strategies that address both biological and psychological components of symptom experience.

Diagnostic testing approaches

The diagnosis of NCGS remains challenging due to the absence of definitive biomarkers and the heterogenous nature of patient symptoms. Although the 2015 Salerno experts' criteria[10] propose a systematic diagnostic approach, including a defined response to a gluten-free diet followed by a gluten challenge, practical implementation faces several obstacles. Expert consensus increasingly emphasises that diagnosis requires more than self-reporting, necessitating structured evaluation protocols.

The controlled dietary evaluation phase (phase 3; figure 2) represents the gold standard for verifying NCGS in the absence of specific biomarkers. Although double-blind, placebo-controlled challenges remain the research gold standard, their clinical implementation is limited by a scarcity of standard gluten vehicles, the wide variability in dosing (ranging from 2 g/day to 52 g/day),[22,74] and differing administration methods (eg, gluten powder cooked into whole foods,[22] bread or muffins,[75,76] muesli bars,[23] or in capsules).[17,74,77,78] In clinical practice, a pragmatic, open elimination-reintroduction protocol might be more feasible. This protocol typically involves an initial gluten-free trial (ideally incorporating FODMAP reduction),[22] followed—if symptoms improve—by structured gluten reintroduction with low-FODMAP, gluten-containing foods. Whereas purified gluten is used in research, clinical alternatives—although not yet validated in trials—can include carefully selected or homemade seitan (a dense, protein-rich product made from vital wheat gluten, provided it is free from garlic, onion, or other high-FODMAP ingredients) or small portions of low-fructan wheat products, such as

sourdough spelt. Symptom monitoring is essential. Fructan-depleted gluten challenges with a low-FODMAP intake might help differentiate NCGS from FODMAP sensitivity.[23]

Biomarker investigation

Despite extensive research, no reliable biomarkers for NCGS have been established. Various candidates have been investigated, including markers of immune activation (soluble CD14, lipopolysaccharide binding protein),[79] indicators of intestinal damage (fatty acid-binding protein 2),[79] measures of barrier function (zonulin),[80] and antibody responses (IgG subclass reactivity to gluten).[81] Although whole-protein antigliadin antibodies appear in 7–18% of individuals with IBS (without coeliac disease),[82–84] and show associations with various conditions including idiopathic ataxia and neurological manifestations,[38] their specificity for NCGS remains unclear.[85] Available markers lack sufficient sensitivity and specificity for routine clinical use and require further validation through large-scale studies.

This three-phase systematic approach balances rigorous evaluation with practical feasibility, while acknowledging that our understanding of NCGS continues to evolve. Once a presumptive diagnosis is established through this process, appropriate management strategies can be implemented based on individual symptom patterns, triggers, and comorbidities.

Management

Dietary management

For individuals with symptomatic responses attributed to gluten or wheat, dietary modification remains the most common management approach, despite ongoing uncertainty about NCGS as a distinct entity and its underlying mechanisms. The heterogeneity of NCGS suggests that different subgroups might respond to different dietary interventions. Although some individuals might react specifically to gluten, evidence from controlled trials indicates that many symptoms improve on a gluten-free diet due to a concurrent reduction in FODMAP intake,[22] particularly fructans, which commonly co-occur with gluten in cereals and grains.[86]

Implementing and maintaining a gluten-free diet presents considerable challenges, including higher costs (gluten-free products cost 139% more than their wheat-based counterparts), increased preparation time, and social restrictions when dining out.[87] These factors contribute to reduced quality-of-life scores, similar to findings in patients with coeliac disease.[87]

Nutritional adequacy warrants careful consideration as gluten-free products often contain less fibre and fewer micronutrients (vitamin D, vitamin B12, and folate) and minerals (iron, zinc, magnesium, and calcium) than their gluten-containing counterparts.[88] This concern is particularly relevant given that patients with NCGS often report multiple food triggers beyond gluten, potentially leading to more restrictive diets. A dietitian who is knowledgeable about gluten-related disorders can provide valuable guidance on maintaining a balanced diet, despite these multiple restrictions.

The optimal amount of gluten restriction remains unclear for NCGS. This uncertainty has practical implications, as any degree of gluten tolerance could substantially improve dietary flexibility by allowing the consumption of products with trace gluten content. Notably, the Codex Alimentarius gluten-free standard (≤20 parts per million) was developed specifically for individuals with coeliac disease;[89] however, its applicability to people with NCGS remains unclear given the absence of validated biomarkers or known thresholds for gluten reactivity in this population. Evidence suggests some individuals with self-reported NCGS can tolerate selected wheat varieties: de Graaf and colleagues showed successful consumption of breads made from spelt or emmer in many participants.[90] This differential tolerability can be explained by the low fructan content in ancient wheat varieties such as spelt,[86] further supporting the role of FODMAPs in symptom generation. Improved labelling of FODMAP content might assist consumers in identifying potential symptom triggers. As tolerance varies between individuals, personalised dietary management—ideally with dietetic guidance—remains essential.

Evidence-based supportive approaches

Beyond dietary management, addressing psychological factors might benefit patients with suspected NCGS. Given the statistically significant nocebo component identified in controlled trials,[4,22] cognitive behavioural therapy[91] and gut-directed hypnotherapy[92] (both proven effective in IBS) might help address symptom-related anxiety and altered visceral perception. Gradual exposure to feared foods in controlled quantities might serve as an alternative or complement to strict exclusion diets,[93] particularly for patients with heightened symptom vigilance. These approaches have shown promise in alleviating both gastrointestinal and extraintestinal symptoms such as depression, impaired general functioning, and fibromyalgia.[94,95]

Emerging approaches

Supplementary approaches, such as enzyme preparations, have unclear value given there has been little evidence for gluten-specific effects[96,97] and emerging strategies, such as wheat fermentation, require further validation before clinical implementation.[98,99]

Integrated approach

A balanced approach to NCGS management integrates appropriate dietary modifications with patient education about the gut–brain connection and the role of expectations in symptom generation. This personalised

framework helps individuals to identify and manage their unique symptom triggers, while avoiding unnecessarily restrictive diets and excessive medicalisation. By acknowledging both the physiological and psychological components of symptom experience, clinicians can support patients in developing sustainable strategies that improve quality of life while respecting individual needs, preferences, and circumstances.

The structure of gluten and wheat

Wheat grain proteins are complex, covering multiple proteins primarily classified as gluten—ie, the major storage protein—and non-gluten proteins. Non-gluten proteins consist of albumins and globulins, including, among others, enzymes (eg, amylases), defence proteins (eg, amylase inhibitors), and puroindolines.

Gluten, strictly defined, is the rubbery protein mass that remains after washing wheat dough to remove starch granules and water-soluble constituents.[13] In wheat, gluten contains alcohol-soluble gliadins and alcohol-insoluble glutenins, which together account for 70–80% of the wheat grain protein content. Although proteins in rye (secalins) and barley (hordeins) show structural similarity and trigger coeliac disease responses, they are not gluten proteins. Gluten is known for its viscoelastic and adhesive properties, which are essential for dough formation and bread making.[100] Polymeric glutenins contain high and low molecular weight subunits, whereas gliadins are made up of types α, β, γ, and ω. These proteins are rich in proline and glutamine amino acids,[101] making them resistant to gastrointestinal proteases. This resistance results in various gluten peptides persisting in the intestinal lumen, with potential bioactive effects.

Most wheat consumption (~95%) involves hexaploid bread wheat (*Triticum aestivum*; genome AABBDD), followed by tetraploid durum wheat (*Triticum durum;* genome AABB). Ancient varieties, such as einkorn (genome AA), emmer (genome AABB), spelt (genome AABBDD), and Khorasan wheat (genome AABB), play a minor role. Claims about the health benefits of ancient wheats are not scientifically supported. Although intensive breeding has affected grain composition by increasing starch and decreasing protein content, elevated immunogenicity is not indicated in modern cultivars.[11,12,102]

Beyond proteins, wheat is an important source of fibres, minerals, vitamins, and phytochemicals. Fermentable fibres, particularly fructans, have emerged as significant symptom triggers in individuals with suspected NCGS.[23] This finding aligns with studies showing no effect of gluten when properly controlled for FODMAP content, and symptom improvement in patients with NCGS on a low-FODMAP diet.[22,31]

Non-gluten proteins, such as amylase trypsin inhibitors (ATIs), represent about 2·5–6·3% of wheat grain proteins and contribute to natural defence in plants.[103] ATIs have shown innate immune activation in vitro[104–106] and in animal models[107,108] via TLR4-mediated pathways,[109] but their clinical relevance in human NCGS remains largely unstudied. No controlled human challenges have directly assessed ATI-specific responses in patients with NCGS. ATIs typically co-precipitate with gluten during extraction, making interpretation of gluten challenge studies more complex. This absence of human clinical data means that, despite promising preclinical findings, ATIs cannot yet be definitively implicated as causal agents in NCGS.

Vital gluten, a concentrated protein extract from wheat flour, is often used in food processing and clinical research for controlled gluten challenges. It is a purified form of wheat protein containing starch and with minimal moisture, but still including other proteins, such as ATIs, which might confound interpretation of clinical study results.[103,105] A 10 g daily dose of vital gluten is sufficient for immune activation in coeliac disease[110] and, when prepared appropriately, is low in FODMAPs (fructans), making it suitable for use in double-blind, placebo-controlled food challenges. Sham or placebo comparators in such trials should match in appearance, texture, and FODMAP content, and commonly consist of gluten-free protein bases, such as rice or maize starches or whey protein isolate, provided they are low in fermentable carbohydrates.

Mechanistic pathways

The pathophysiology of NCGS remains poorly understood, with evidence from human, animal, and in-vitro studies suggesting multiple potential mechanisms (figure 3). Scientific developments have challenged earlier assumptions about immune mechanisms in NCGS. Although rapid symptom onset was previously hypothesised to indicate innate immune involvement distinct from adaptive responses in coeliac disease, direct experimental evidence from controlled human studies has not supported this distinction. Studies on coeliac disease have shown that gluten can rapidly induce symptoms, particularly nausea, accompanied by systemic cytokine release, indicating gluten-specific T-cell activation within hours.[111–113] New diagnostic approaches measuring gluten-stimulated IL-2 release now permit differentiation between coeliac disease and NCGS, even in individuals on a gluten-free diet, by detecting gluten-specific adaptive immune activation present only in coeliac disease.[114] These findings indicate that early symptom onset alone does not imply innate immune activation. By contrast, human challenge studies on NCGS have consistently found no increase in systemic cytokine release following gluten exposure,[115–117] highlighting the importance of distinguishing the mechanisms in NCGS from those extrapolated with preclinical models. The bolus gluten challenge protocol, used in coeliac disease by Daveson and colleagues,[110] could be a valuable model to investigate acute symptom generation and immune responses in

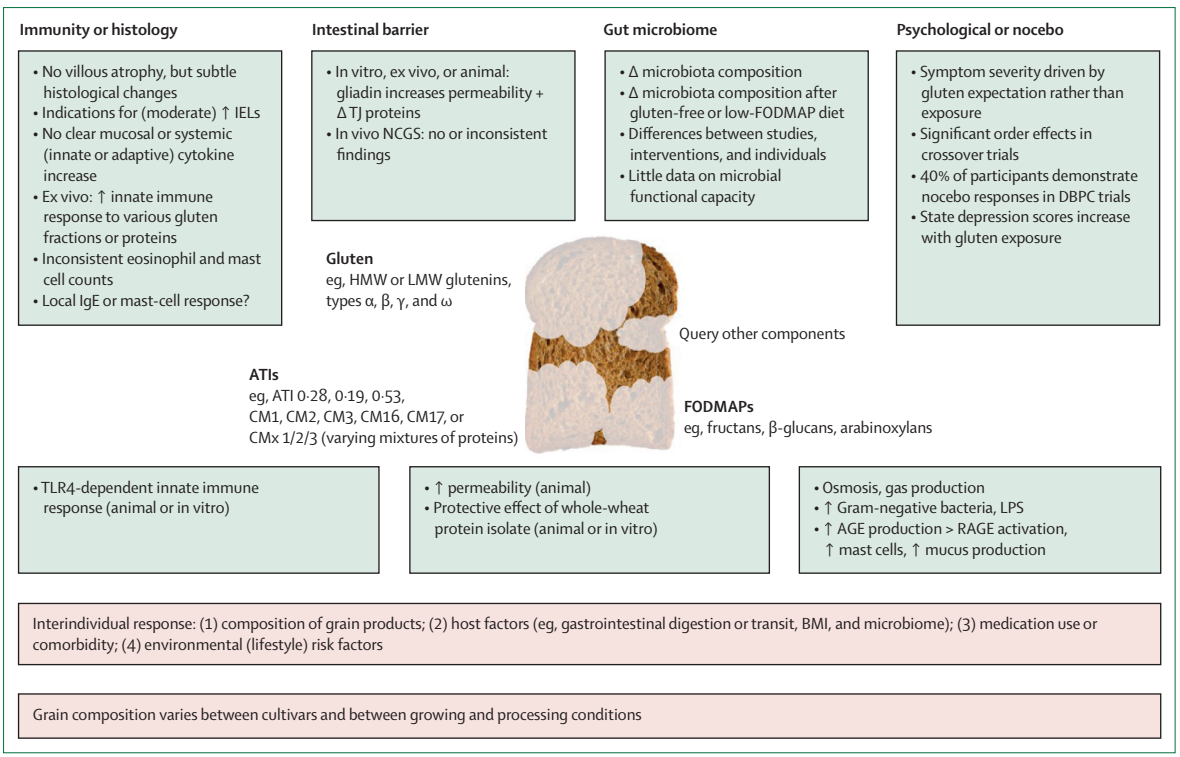

Figure 3: **Potential pathophysiological mechanisms**
For ATIs, the evidence is from preclinical studies only. IEL=intraepithelial lymphocyte. TJ=tight junction. NCGS=non-coeliac gluten sensitivity. FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. DBPC=double-blind, placebo-controlled. HMW=high molecular weight. LMW=low molecular weight. ATI=amylase trypsin inhibitor. LPS=lipopolysaccharide. AGE=advanced glycation endproducts. RAGE=receptor for advanced glycation endproducts.

NCGS under rigorously controlled conditions. Beyond immune mechanisms, several other pathways have been proposed to explain symptom generation in NCGS.

The four key pathways that have been investigated, namely, psychological factors, immune activation, intestinal barrier function, and gut microbiota alterations, are illustrated in figure 3. Psychological factors appear central to symptom generation through expectancy effects[4,22] and altered visceral perception, although the mechanisms interact in a complex way with biological pathways. Whereas earlier studies explored possible local immune changes in NCGS, most methodologically robust investigations have not shown consistent mucosal irregularities or systemic immune activation.[48,118–120] Evidence for barrier dysfunction is similarly conflicting: some studies report increased intestinal permeability markers[79,80] and others show no changes in functional barrier tests.[29,115,117,121] Microbiota studies suggest possible alterations in bacterial composition with gluten or wheat intake, although findings vary between populations.[31,122–125] The failure to replicate findings, compounded by methodological variability and inconsistent definitions, suggests that NCGS might reflect a spectrum of gut–brain interaction disorders and psychological factors, rather than a discrete gluten-mediated condition. Unlike coeliac disease, no genetic associations have been established to support NCGS as a distinct immunogenetic entity. Although ATIs have shown immune effects in preclinical studies, no controlled human studies have directly examined their role in NCGS symptom generation. A detailed discussion of the current evidence for each proposed mechanistic pathway, including the strengths and weaknesses of human versus preclinical studies, is provided in appendix 2 (pp 2–6).

See Online for appendix 2

The complex and potentially heterogeneous nature of NCGS might help explain why only some individuals show specific gluten reactivity in controlled challenges. Although large, well designed clinical studies have not supported NCGS as a distinct entity to date, the possibility of the specific physiological effects of gluten or wheat in subgroups cannot be excluded. Future research should include both large-scale, non-hypothesis-driven approaches, such as systems-level genetic, metabolic, immunological, and microbiome profiling, and smaller, hypothesis-driven studies targeting specific mechanistic pathways, provided a viable hypothesis is clearly defined and rigorously tested.

Challenges and solutions to understanding NCGS

The most fundamental challenge in NCGS research is uncertainty about its existence as a distinct clinical entity.

Panel: **Key challenges and proposed solutions in non-coeliac gluten sensitivity research, diagnosis, and management**

Methodological limitations in clinical trials

Challenge

Double-blind placebo-controlled (DBPC) trials in non-coeliac gluten sensitivity (NCGS) are hampered by inconsistent coeliac disease screening,[74,77] poor control of nocebo effects, and non-standard protocols

Suggested solutions

- Implement uniform diagnostic criteria for coeliac disease exclusion
- Standardise challenge protocols (vehicle, washout periods, and blinding verification)
- Develop measures to account for nocebo responses
- Establish consistent outcome assessment across trials

Lack of reliable diagnostic criteria

Challenge

Current diagnostic criteria are complex; the absence of biomarkers for NCGS leads to self-diagnosis, unclear prevalence estimates, and heterogenous study populations

Suggested solutions

- Develop validated diagnostic criteria with expert consensus
- Identify objective biomarkers for accurate NCGS diagnosis
- Do population-based studies with standardised assessment methods

Dietary restriction consequences

Challenge

Self-directed dietary restriction often leads to nutritional inadequacies and unnecessary restrictions

Suggested solutions

- Involve dietitians early in the diagnostic process
- Implement systematic dietary challenge protocols controlling for fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs)
- Monitor nutritional status during restriction diets
- Consider psychological or gastroenterological referral when features of disordered eating or avoidant/restrictive food intake disorder are present

Commercial influences

Challenge

Commercial and media influences can distort research priorities, diagnostic criteria, and patient management

Suggested solutions

- Require transparent declaration of funding sources
- Develop independent diagnostic criteria
- Consider commercial determinants in guideline development

Heterogeneous research method

Challenge

Inconsistent study designs and diagnostic criteria prevent meaningful comparison across studies

Suggested solutions

- Implement standardised diagnostic criteria and study designs
- Do multicentre studies with consistent protocols
- Use strategies to minimise nocebo effects

Mechanisms of action

Challenge

Multiple pathways likely contribute to symptom generation, with substantial individual variability

Suggested solutions

- Investigate wheat components with standardised protocols
- Study individual response variations and gut–brain interactions
- Compare findings with relevant control groups
- Develop integrated models of biological and psychological factors
- Replicate existing studies and explore symptom responses to varied FODMAP sources and doses

Interpretation of gluten challenges

Challenge

Challenges are confounded by wheat complexity and poor standardisation of protocols

Suggested solutions

- Develop best-practice guidelines for gluten challenges
- Control for confounding dietary factors
- Establish clinically significant endpoints
- Test dose–response relationships

Minimising dietary restriction risks

Challenge

Unnecessary dietary restrictions can lead to nutritional deficiencies and misdiagnosis

Suggested solutions

- Raise proper diagnostic testing before gluten-free diet recommendations
- Incorporate nutritional counselling with dietary modification
- Implement education about the risks of self-diagnosis

Management and follow-up

Challenge

The long-term health impacts of NCGS remain unknown, with insufficient evidence-based guidelines

Suggested solutions

- Develop multidisciplinary management approaches
- Do longitudinal cohort studies of health outcomes
- Create and validate NCGS-specific outcome measures

Multiple barriers impede not only progress in understanding and managing this condition, but also in establishing whether it represents a unique disorder rather than a subset of other conditions.

Although approximately 10% of adults self-report gluten or wheat sensitivity,[24] controlled trials show gluten-specific responses in only a few.[2,3] This discrepancy raises essential questions about whether NCGS exists as currently conceptualised. The substantial overlap with DGBI, powerful nocebo effects, and evidence implicating FODMAPs rather than gluten in symptom generation, suggest that current understanding might need substantial revision.

Similar to challenges faced in other areas of nutrition research,[6] commercial influences in NCGS extend beyond direct research funding to include structural mechanisms shaping scientific and public discourse.[7,126] The growing gluten-free market creates powerful incentives for emphasising gluten sensitivity in the media, education, and clinical practice,[126] manifesting as selective amplification of positive findings regarding gluten-free diets. These market forces can subtly influence research priorities, shape patient expectations and clinician perceptions, and potentially contribute to nocebo effects.[7] Addressing these challenges requires independent, well designed studies examining specific wheat components while controlling for bias, critical evaluation of information sources, and transparent communication with patients about the current evidence regarding gluten or wheat sensitivity.

Integration of emerging research methods offers promising solutions for addressing these fundamental questions. Experimental developments to assess gut–brain axis dysfunction[127] alongside advances in microbiome analysis,[128] immune profiling,[116] and psychological assessment[4] provide opportunities for a more comprehensive understanding of individual variation in symptom triggers and treatment response. These approaches could help identify whether distinct patient subgroups exist who show specific wheat component sensitivity, or whether the reported symptoms reflect the broader mechanisms of gut–brain interaction.

Implementation of evidence-based care remains challenging given the underlying uncertainty about the nature of this condition. The development of standardised clinical paths should balance rigorous diagnostic evaluation with practical feasibility and increasing pressure on health care, while acknowledging that our understanding of NCGS might evolve substantially. These clinical paths should include careful consideration of how to systematically assess both biological and psychological factors while maintaining patient-centred care.

Looking ahead, technological advances might facilitate more precise diagnosis and monitoring, but immediate focus should remain on resolving fundamental questions about NCGS as a distinct entity. Progress will require integrating mechanistic insights with patient experience, while upholding scientific rigour in the face of commercial pressures. Prioritising key research areas while addressing methodological challenges offers the most promising path towards understanding whether and how NCGS exists as a unique condition (panel).

Conclusion

The term NCGS is used to describe a heterogeneous group of individuals reporting intestinal and extraintestinal symptoms related to gluten or wheat ingestion, in the absence of coeliac disease or wheat allergy. However, whether NCGS represents a distinct clinical entity remains unclear. Meta-analyses indicate that only a small subgroup of people show gluten-specific responses in controlled trials, with evidence suggesting that FODMAPs and nocebo effects contribute significantly to symptom generation. Commercial influences, particularly from the growing gluten-free market, can subtly shape research priorities and narrative construction around NCGS. Definitive diagnosis remains elusive due to the absence of biomarkers, considerable overlap with DGBI, and methodological challenges in dietary evaluation. The role of specific wheat components, such as gluten, fructans, and ATIs, in triggering symptoms requires further investigation in well designed, independent studies. Until causative agents are identified and diagnostic tests developed, NCGS remains a diagnosis of exclusion, requiring careful systematic evaluation. Current evidence supports a multidisciplinary approach that integrates dietary modifications with psychological support while ensuring nutritional adequacy.

Contributors

JRB conceptualised, administered, and supervised the project, and performed the initial literature search. Each author contributed to writing—original draft by preparing key sections of the manuscript. All authors contributed to data curation by extracting data and collaboratively developing the tables, figures, and panels. JRB and CC accessed the data used in the tables. IA and DJ accessed source data to inform content development. All authors contributed to data verification. All authors contributed to data interpretation, writing—review and editing, and approved the final version of the manuscript.

Declaration of interests

JRB reports research funding from the Rome Foundation and Yakult, speaker honoraria from the American Gastroenterological Association and Asia Pacific Clinical Nutrition Society, and unpaid editorial and leadership roles with the Nutrition Society of Australia and the Australasian Neurogastroenterology & Motility Association. DJ reports research funding through public–private partnership grants from TKI Agri & Food, Health Holland, the NWO-CCC Carbokinetics programme, Organic A2BV/Mothersfinest BV, and the EU Horizon 2020 programme (DISCOvERIE #848228). IA reports research funding and honoraria from PrecisionBiotics, Tillotts, and the Rome Foundation, and serves as a Section Editor for Gastroenterology. CC reports honoraria from Takeda, GSK, and Thermo Fisher Scientific. We note that these interests were all unrelated to the submitted work.

Acknowledgments

We thank Jason Tye-Din (Walter and Eliza Hall Institute of Medical Research and The University of Melbourne) for his review of the final version of the manuscript. We thank Marlijne de Graaf (Maastricht University) for providing some of the data informing figure 1. JRB is supported by an Australian National Health and Medical Research Council Emerging Leadership Fellowship (APP2025943).

References

1 Aziz I. The global phenomenon of self-reported wheat sensitivity. *Am J Gastroenterol* 2018; **113:** 945–48.

2 Lionetti E, Pulvirenti A, Vallorani M, et al. Re-challenge studies in non-celiac gluten sensitivity: a systematic review and meta-analysis. *Front Physiol* 2017; **8:** 621.

3 Borrelli de Andreis F, Schiepatti A, Gibiino G, Fabbri C, Baiardi P, Biagi F. Is it time to rethink the burden of non-coeliac gluten sensitivity? A systematic review. *Minerva Gastroenterol* 2022; **68:** 442–49.

4 de Graaf MCG, Lawton CL, Croden F, et al. The effect of expectancy versus actual gluten intake on gastrointestinal and extra-intestinal symptoms in non-coeliac gluten sensitivity: a randomised, double-blind, placebo-controlled, international, multicentre study. *Lancet Gastroenterol Hepatol* 2024; **9:** 110–23.

5 MarketsAndMarkets. Gluten-free products market size, share & trends analysis. Sept, 2024. https://www.marketsandmarkets.com/Market-Reports/gluten-free-products-market-738.html#:~:text=Overview,at%20a%20CAGR%20of%208.3%25 (accessed Feb 24, 2025).

6 Lacy-Nichols J, Nandi S, Mialon M, et al. Conceptualising commercial entities in public health: beyond unhealthy commodities and transnational corporations. *Lancet* 2023; **401:** 1214–28.

7 Gilmore AB, Fabbri A, Baum F, et al. Defining and conceptualising the commercial determinants of health. *Lancet* 2023; **401:** 1194–213.

8 Nash DT, Slutzky AR. Gluten sensitivity: new epidemic or new myth? *Proc Bayl Univ Med Cent* 2014; **27:** 377–78.

9 Legg T, Hatchard J, Gilmore AB. The science for profit model—how and why corporations influence science and the use of science in policy and practice. *PLoS One* 2021; **16:** e0253272.

10 Catassi C, Elli L, Bonaz B, et al. Diagnosis of non-celiac gluten sensitivity (NCGS): the Salerno Experts' criteria. *Nutrients* 2015; **7:** 4966–77.

11 Pronin D, Börner A, Weber H, Scherf KA. Wheat (*Triticum aestivum* L.) breeding from 1891 to 2010 contributed to increasing yield and glutenin contents but decreasing protein and gliadin contents. *J Agric Food Chem* 2020; **68:** 13247–56.

12 Geisslitz S, Pronin D, Neerukonda M, et al. Breeding from 1891 to 2010 did not increase the content of amylase/trypsin-inhibitors in wheat (*Triticum aestivum*). *NPJ Sci Food* 2023; **7:** 43.

13 Kasarda DD. Can an increase in celiac disease be attributed to an increase in the gluten content of wheat as a consequence of wheat breeding? *J Agric Food Chem* 2013; **61:** 1155–59.

14 Ellis A, Linaker BD. Non-coeliac gluten sensitivity? *Lancet* 1978; **311:** 1358–59.

15 Cooper BT, Holmes GK, Ferguson R, Thompson RA, Allan RN, Cooke WT. Gluten-sensitive diarrhea without evidence of celiac disease. *Gastroenterology* 1980; **79:** 801–06.

16 Verdu EF, Armstrong D, Murray JA. Between celiac disease and irritable bowel syndrome: the "no man's land" of gluten sensitivity. *Am J Gastroenterol* 2009; **104:** 1587–94.

17 Carroccio A, Rini G, Mansueto P. Non-celiac wheat sensitivity is a more appropriate label than non-celiac gluten sensitivity. *Gastroenterology* 2014; **146:** 320–21.

18 Catassi C, Catassi G, Naspi L. Nonceliac gluten sensitivity. *Curr Opin Clin Nutr Metab Care* 2023; **26:** 490–94.

19 Tavakkoli A, Lewis SK, Tennyson CA, Lebwohl B, Green PHR. Characteristics of patients who avoid wheat and/or gluten in the absence of celiac disease. *Dig Dis Sci* 2014; **59:** 1255–61.

20 Potter MDE, Duncanson K, Jones MP, Walker MM, Keely S, Talley NJ. Wheat sensitivity and functional dyspepsia: a pilot, double-blind, randomized, placebo-controlled dietary crossover trial with novel challenge protocol. *Nutrients* 2020; **12:** 1947.

21 Newberry C, McKnight L, Sarav M, Pickett-Blakely O. Going gluten free: the history and nutritional implications of today's most popular diet. *Curr Gastroenterol Rep* 2017; **19:** 54.

22 Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. *Gastroenterology* 2013; **145:** 320–28.

23 Skodje GI, Sarna VK, Minelle IH, et al. Fructan, rather than gluten, induces symptoms in patients with self-reported non-celiac gluten sensitivity. *Gastroenterology* 2018; **154:** 529–39.

24 Aziz I, Lewis NR, Hadjivassiliou M, et al. A UK study assessing the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care. *Eur J Gastroenterol Hepatol* 2014; **26:** 33–39.

25 Volta U, Bardella MT, Calabrò A, Troncone R, Corazza GR, and the Study Group for Non-Celiac Gluten Sensitivity. An Italian prospective multicenter survey on patients suspected of having non-celiac gluten sensitivity. *BMC Med* 2014; **12:** 85.

26 Nwaru BI, Hickstein L, Panesar SS, et al, and the EAACI Food Allergy and Anaphylaxis Guidelines Group. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy* 2014; **69:** 62–75.

27 Catassi C, Verdu EF, Bai JC, Lionetti E. Coeliac disease. *Lancet* 2022; **399:** 2413–26.

28 An C, Yang J, Pinto-Sanchez MI, et al. Molecular triggers of non-celiac wheat sensitivity: a scoping review and analysis. *Am J Gastroenterol* 2025; **120:** 1998–2008.

29 Iven J, Geeraerts A, Vanuytsel T, Tack J, Van Oudenhove L, Biesiekierski JR. Impact of acute and sub-acute gluten exposure on gastrointestinal symptoms and psychological responses in non-coeliac gluten sensitivity: a randomised crossover study. *United European Gastroenterol J* 2025; **13:** 1295–1306.

30 Böhn L, Störsrud S, Törnblom H, Bengtsson U, Simrén M. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. *Am J Gastroenterol* 2013; **108:** 634–41.

31 Dieterich W, Schuppan D, Schink M, et al. Influence of low FODMAP and gluten-free diets on disease activity and intestinal microbiota in patients with non-celiac gluten sensitivity. *Clin Nutr* 2019; **38:** 697–707.

32 Fernandes Dias LB de A, Kobus RA, Bagolin do Nascimento A. Effectiveness of the low-FODMAP diet in improving non-celiac gluten sensitivity: a systematic review. *Br J Nutr* 2023; **129:** 2067–75.

33 Arranz LI, Canela MÁ, Rafecas M. Dietary aspects in fibromyalgia patients: results of a survey on food awareness, allergies, and nutritional supplementation. *Rheumatol Int* 2012; **32:** 2615–21.

34 Uhde M, Indart AC, Yu XB, et al. Markers of non-coeliac wheat sensitivity in patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Gut* 2019; **68:** 377–78.

35 Croall ID, Hoggard N, Aziz I, Hadjivassiliou M, Sanders DS. Brain fog and non-coeliac gluten sensitivity: proof of concept brain MRI pilot study. *PLoS One* 2020; **15:** e0238283.

36 Peters SL, Biesiekierski JR, Yelland GW, Muir JG, Gibson PR. Randomised clinical trial: gluten may cause depression in subjects with non-coeliac gluten sensitivity—an exploratory clinical study. *Aliment Pharmacol Ther* 2014; **39:** 1104–12.

37 Bonciolini V, Bianchi B, Del Bianco E, Verdelli A, Caproni M. Cutaneous manifestations of non-celiac gluten sensitivity: clinical histological and immunopathological features. *Nutrients* 2015; **7:** 7798–805.

38 Hadjivassiliou M, Sanders DS, Grünewald RA, Woodroofe N, Boscolo S, Aeschlimann D. Gluten sensitivity: from gut to brain. *Lancet Neurol* 2010; **9:** 318–30.

39 Makharia A, Catassi C, Makharia GK. The overlap between irritable bowel syndrome and non-celiac gluten sensitivity: a clinical dilemma. *Nutrients* 2015; **7:** 10417–26.

40 Biesiekierski JR, Newnham ED, Shepherd SJ, Muir JG, Gibson PR. Characterization of adults with a self-diagnosis of nonceliac gluten sensitivity. *Nutr Clin Pract* 2014; **29:** 504–09.

41 Aziz I, Hadjivassiliou M, Sanders DS. The spectrum of noncoeliac gluten sensitivity. *Nat Rev Gastroenterol Hepatol* 2015; **12:** 516–26.

42 Potter MDE, Walker MM, Jones MP, Koloski NA, Keely S, Talley NJ. Wheat intolerance and chronic gastrointestinal symptoms in an Australian population-based study: association between wheat sensitivity, celiac disease and functional gastrointestinal disorders. *Am J Gastroenterol* 2018; **113:** 1036–44.

43 van Gils T, Nijeboer P, IJssennagger CE, Sanders DS, Mulder CJJ, Bouma G. Prevalence and characterization of self-reported gluten sensitivity in The Netherlands. *Nutrients* 2016; **8:** 714.

44 Skodje GI, Minelle IH, Rolfsen KL, et al. Dietary and symptom assessment in adults with self-reported non-coeliac gluten sensitivity. *Clin Nutr ESPEN* 2019; **31:** 88–94.

45 Shiha MG, Aziz I. Review article: physical and psychological comorbidities associated with irritable bowel syndrome. *Aliment Pharmacol Ther* 2021; **54** (suppl 1)**:** s12–23.

46 Lind R, Arslan G, Eriksen HR, et al. Subjective health complaints and modern health worries in patients with subjective food hypersensitivity. *Dig Dis Sci* 2005; **50:** 1245–51.

47 Berstad A, Undseth R, Lind R, Valeur J. Functional bowel symptoms, fibromyalgia and fatigue: a food-induced triad? *Scand J Gastroenterol* 2012; **47:** 914–19.

48 Hadjivassiliou M, Rao DG, Grìnewald RA, et al. Neurological dysfunction in coeliac disease and non-coeliac gluten sensitivity. *Am J Gastroenterol* 2016; **111:** 561–67.

49 Edwards George JB, Aideyan B, Yates K, et al. Gluten-induced neurocognitive impairment: results of a nationwide study. *J Clin Gastroenterol* 2022; **56:** 584–91.

50 Zis P, Hadjivassiliou M. Treatment of neurological manifestations of gluten sensitivity and coeliac disease. *Curr Treat Options Neurol* 2019; **21:** 10.

51 Zanini B, Baschè R, Ferraresi A, et al. Randomised clinical study: gluten challenge induces symptom recurrence in only a minority of patients who meet clinical criteria for non-coeliac gluten sensitivity. *Aliment Pharmacol Ther* 2015; **42:** 968–76.

52 Carroccio A, D'Alcamo A, Cavataio F, et al. High proportions of people with nonceliac wheat sensitivity have autoimmune disease or antinuclear antibodies. *Gastroenterology* 2015; **149:** 596–603.

53 Losurdo G, Principi M, Iannone A, et al. Extra-intestinal manifestations of non-celiac gluten sensitivity: an expanding paradigm. *World J Gastroenterol* 2018; **24:** 1521–30.

54 Volta U, Tovoli F, Cicola R, et al. Serological tests in gluten sensitivity (nonceliac gluten intolerance). *J Clin Gastroenterol* 2012; **46:** 680–85.

55 Carroccio A, Soresi M, D'Alcamo A, et al. Risk of low bone mineral density and low body mass index in patients with non-celiac wheat-sensitivity: a prospective observation study. *BMC Med* 2014; **12:** 230.

56 Zingone F, Bartalini C, Siniscalchi M, et al. Alterations in diets of patients with nonceliac gluten sensitivity compared with healthy individuals. *Clin Gastroenterol Hepatol* 2017; **15:** 63–68.

57 Staller K, Abber SR, Burton Murray H. The intersection between eating disorders and gastrointestinal disorders: a narrative review and practical guide. *Lancet Gastroenterol Hepatol* 2023; **8:** 565–78.

58 Lee ECK, Trogen B, Brady K, Ford LS, Wang J. The natural history and risk factors for the development of food allergies in children and adults. *Curr Allergy Asthma Rep* 2024; **24:** 121–31.

59 Santos AF, Riggioni C, Agache I, et al. EAACI guidelines on the diagnosis of IgE-mediated food allergy. *Allergy* 2023; **78:** 3057–76.

60 Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, and the EAACI Food Allergy and Anaphylaxis Guidelines Group. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy* 2014; **69:** 992–1007.

61 Savage J, Johns CB. Food allergy: epidemiology and natural history. *Immunol Allergy Clin North Am* 2015; **35:** 45–59.

62 du Pre MF, Iversen R, Sollid LM. Coeliac disease: the paradox of diagnosing a food hypersensitivity disorder with autoantibodies. *Gut* 2024; **73:** 844–53.

63 Vermeersch P, Geboes K, Mariën G, Hoffman I, Hiele M, Bossuyt X. Serological diagnosis of celiac disease: comparative analysis of different strategies. *Clin Chim Acta* 2012; **413:** 1761–67.

64 Lebwohl B, Sanders DS, Green PHR. Coeliac disease. *Lancet* 2018; **391:** 70–81.

65 Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology guidelines update: diagnosis and management of celiac disease. *Am J Gastroenterol* 2023; **118:** 59–76.

66 Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. *Gut* 2013; **62:** 43–52.

67 Al-Toma A, Volta U, Auricchio R, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United European Gastroenterol J* 2019; **7:** 583–613.

68 Husby S, Koletzko S, Korponay-Szabó I, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition guidelines for diagnosing coeliac disease 2020. *J Pediatr Gastroenterol Nutr* 2020; **70:** 141–56.

69 Aziz I, Branchi F, Pearson K, Priest J, Sanders DS. A study evaluating the bidirectional relationship between inflammatory bowel disease and self-reported non-celiac gluten sensitivity. *Inflamm Bowel Dis* 2015; **21:** 847–53.

70 Herfarth HH, Martin CF, Sandler RS, Kappelman MD, Long MD. Prevalence of a gluten-free diet and improvement of clinical symptoms in patients with inflammatory bowel diseases. *Inflamm Bowel Dis* 2014; **20:** 1194–97.

71 Janssen LM, Rezazadeh Ardabili A, Romberg-Camps MJL, et al. Abdominal pain in patients with inflammatory bowel disease in remission: a prospective study on contributing factors. *Aliment Pharmacol Ther* 2023; **58:** 1041–51.

72 Kinsey L, Burden S. A survey of people with inflammatory bowel disease to investigate their views of food and nutritional issues. *Eur J Clin Nutr* 2016; **70:** 852–54.

73 Molina-Infante J, Carroccio A. Suspected nonceliac gluten sensitivity confirmed in few patients after gluten challenge in double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* 2017; **15:** 339–48.

74 Shahbazkhani B, Sadeghi A, Malekzadeh R, et al. Non-celiac gluten sensitivity has narrowed the spectrum of irritable bowel syndrome: a double-blind randomized placebo-controlled trial. *Nutrients* 2015; **7:** 4542–54.

75 Biesiekierski JR, Newnham ED, Irving PM, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol* 2011; **106:** 508–14.

76 Dale HF, Hatlebakk JG, Hovdenak N, Ystad SO, Lied GA. The effect of a controlled gluten challenge in a group of patients with suspected non-coeliac gluten sensitivity: a randomized, double-blind placebo-controlled challenge. *Neurogastroenterol Motil* 2018; **30:** e13332.

77 Elli L, Tomba C, Branchi F, et al. Evidence for the presence of non-celiac gluten sensitivity in patients with functional gastrointestinal symptoms: results from a multicenter randomized double-blind placebo-controlled gluten challenge. *Nutrients* 2016; **8:** 84.

78 Di Sabatino A, Volta U, Salvatore C, et al. Small amounts of gluten in subjects with suspected nonceliac gluten sensitivity: a randomized, double-blind, placebo-controlled, cross-over trial. *Clin Gastroenterol Hepatol* 2015; **13:** 1604–12.

79 Uhde M, Ajamian M, Caio G, et al. Intestinal cell damage and systemic immune activation in individuals reporting sensitivity to wheat in the absence of coeliac disease. *Gut* 2016; **65:** 1930–37.

80 Barbaro MR, Cremon C, Morselli-Labate AM, et al. Serum zonulin and its diagnostic performance in non-coeliac gluten sensitivity. *Gut* 2020; **69:** 1966–74.

81 Uhde M, Caio G, De Giorgio R, Green PH, Volta U, Alaedini A. Subclass profile of IgG antibody response to gluten differentiates nonceliac gluten sensitivity from celiac disease. *Gastroenterology* 2020; **159:** 1965–1967.

82 Sanders DS, Carter MJ, Hurlstone DP, et al. Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care. *Lancet* 2001; **358:** 1504–08.

83 Cash BD, Rubenstein JH, Young PE, et al. The prevalence of celiac disease among patients with nonconstipated irritable bowel syndrome is similar to controls. *Gastroenterology* 2011; **141:** 1187–93.

84 Ahmed A, Dixit K, Singh A, et al. Sieving out non-celiac gluten sensitivity amongst patients with irritable bowel syndrome. *Dig Liver Dis* 2024; **56:** 451–57.

85 Volta U, De Giorgio R. New understanding of gluten sensitivity. *Nat Rev Gastroenterol Hepatol* 2012; **9:** 295–99.

86 Biesiekierski JR, Rosella O, Rose R, et al. Quantification of fructans, galacto-oligosacharides and other short-chain carbohydrates in processed grains and cereals. *J Hum Nutr Diet* 2011; **24:** 154–76.

87 Bozorg SR, Lee AR, Mårild K, Murray JA. The economic iceberg of celiac disease: more than the cost of gluten-free food. *Gastroenterology* 2024; **167:** 172–82.

88 Wild D, Robins GG, Burley VJ, Howdle PD. Evidence of high sugar intake, and low fibre and mineral intake, in the gluten-free diet. *Aliment Pharmacol Ther* 2010; **32:** 573–81.

89 Codex Alimentarius. Standard for foods for special dietary use for persons intolerant to gluten. 2008. https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCXS%2B118-1979%252FCXS_118e_2015.pdf (accessed Feb 21, 2025).

90 de Graaf MC, Timmers E, Bonekamp B, et al. Two randomized crossover multicenter studies investigating gastrointestinal symptoms after bread consumption in individuals with noncoeliac wheat sensitivity: do wheat species and fermentation type matter? *Am J Clin Nutr* 2024; **119:** 896–907.

91 Black CJ, Thakur ER, Houghton LA, Quigley EMM, Moayyedi P, Ford AC. Efficacy of psychological therapies for irritable bowel syndrome: systematic review and network meta-analysis. *Gut* 2020; **69:** 1441–51.

92 Peters SL, Yao CK, Philpott H, Yelland GW, Muir JG, Gibson PR. Randomised clinical trial: the efficacy of gut-directed hypnotherapy is similar to that of the low FODMAP diet for the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2016; **44:** 447–59.

93 Biesiekierski JR, Manning LP, Murray HB, Vlaeyen JWS, Ljótsson B, Van Oudenhove L. Review article: exclude or expose? The paradox of conceptually opposite treatments for irritable bowel syndrome. *Aliment Pharmacol Ther* 2022; **56:** 592–605.

94 Ljótsson B, Falk L, Vesterlund AW, et al. Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome—a randomized controlled trial. *Behav Res Ther* 2010; **48:** 531–39.

95 Hedman-Lagerlöf M, Hedman-Lagerlöf E, Axelsson E, et al. Internet-delivered exposure therapy for fibromyalgia: a randomized controlled trial. *Clin J Pain* 2018; **34:** 532–42.

96 Ido H, Matsubara H, Kuroda M, et al. Combination of gluten-digesting enzymes improved symptoms of non-celiac gluten sensitivity: a randomized single-blind, placebo-controlled crossover study. *Clin Transl Gastroenterol* 2018; **9:** e181.

97 Scricciolo A, Lombardo V, Elli L, et al. Use of a proline-specific endopeptidase to reintroduce gluten in patients with non-coeliac gluten sensitivity: a randomized trial. *Clin Nutr* 2022; **41:** 2025–30.

98 Huang X, Schuppan D, Rojas Tovar LE, Zevallos VF, Loponen J, Gänzle M. Sourdough fermentation degrades wheat alpha-amylase/trypsin inhibitor (ATI) and reduces pro-inflammatory activity. *Foods* 2020; **9:** 943.

99 Juhász A, Nye-Wood MG, Tanner GJ, Colgrave ML. Digestibility of wheat alpha-amylase/trypsin inhibitors using a caricain digestive supplement. *Front Nutr* 2022; **9:** 977206.

100 Shewry P. Wheat grain proteins: past, present, and future. *Cereal Chem* 2023; **100:** 9–22.

101 Bromilow S, Gethings LA, Buckley M, et al. A curated gluten protein sequence database to support development of proteomics methods for determination of gluten in gluten-free foods. *J Proteomics* 2017; **163:** 67–75.

102 Brouns F, Geisslitz S, Guzman C, et al. Do ancient wheats contain less gluten than modern bread wheat, in favour of better health? *Nutr Bull* 2022; **47:** 157–67.

103 Geisslitz S, Shewry P, Brouns F, et al. Wheat ATIs: characteristics and role in human disease. *Front Nutr* 2021; **8:** 667370.

104 Cuccioloni M, Mozzicafreddo M, Bonfili L, et al. Interfering with the high-affinity interaction between wheat amylase trypsin inhibitor CM3 and toll-like receptor 4: in silico and biosensor-based studies. *Sci Rep* 2017; **7:** 13169.

105 Junker Y, Zeissig S, Kim SJ, et al. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. *J Exp Med* 2012; **209:** 2395–408.

106 Zevallos VF, Raker V, Tenzer S, et al. Nutritional wheat amylase-trypsin inhibitors promote intestinal inflammation via activation of myeloid cells. *Gastroenterology* 2017; **152:** 1100–13.

107 Zevallos VF, Yogev N, Hauptmann J, et al. Dietary wheat amylase trypsin inhibitors exacerbate CNS inflammation in experimental multiple sclerosis. *Gut* 2024; **73:** 92–104.

108 Caminero A, McCarville JL, Zevallos VF, et al. Lactobacilli degrade wheat amylase trypsin inhibitors to reduce intestinal dysfunction induced by immunogenic wheat proteins. *Gastroenterology* 2019; **156:** 2266–80.

109 Pickert G, Wirtz S, Matzner J, et al. Wheat consumption aggravates colitis in mice via amylase trypsin inhibitor-mediated dysbiosis. *Gastroenterology* 2020; **159:** 257–72.

110 Daveson AJM, Tye-Din JA, Goel G, et al, and the RESET CeD Study Group. Masked bolus gluten challenge low in FODMAPs implicates nausea and vomiting as key symptoms associated with immune activation in treated coeliac disease. *Aliment Pharmacol Ther* 2020; **51:** 244–52.

111 Goel G, Tye-Din JA, Qiao SW, et al. Cytokine release and gastrointestinal symptoms after gluten challenge in celiac disease. *Sci Adv* 2019; **5:** eaaw7756.

112 Tye-Din JA, Daveson AJM, Ee HC, et al. Elevated serum interleukin-2 after gluten correlates with symptoms and is a potential diagnostic biomarker for coeliac disease. *Aliment Pharmacol Ther* 2019; **50:** 901–10.

113 Tye-Din JA, Daveson AJM, Goldstein KE, et al, and the RESET CeD Study Group. Patient factors influencing acute gluten reactions and cytokine release in treated coeliac disease. *BMC Med* 2020; **18:** 362.

114 Moscatelli OG, Russell AK, Henneken LM, et al. Blood-based T-cell diagnosis of celiac disease. *Gastroenterology* 2025; published online June 9. https://doi.org/10.1053/j.gastro.2025.05.022.

115 Dale HF, Johannessen JCH, Brønstad I, Lied GA. Assessment of markers of gut integrity and inflammation in non-celiac gluten sensitivity after a gluten free-diet. *Int J Gen Med* 2021; **14:** 9459–70.

116 Tye-Din JA, Skodje GI, Sarna VK, et al. Cytokine release after gluten ingestion differentiates coeliac disease from self-reported gluten sensitivity. *United European Gastroenterol J* 2020; **8:** 108–18.

117 Cartee AK, Choung RS, King KS, et al. Plasma IL-2 and symptoms response after acute gluten exposure in subjects with celiac disease or nonceliac gluten sensitivity. *Am J Gastroenterol* 2022; **117:** 319–26.

118 Di Sabatino A, Giuffrida P, Fornasa G, et al. Innate and adaptive immunity in self-reported nonceliac gluten sensitivity versus celiac disease. *Dig Liver Dis* 2016; **48:** 745–52.

119 Miglietta S, Borghini R, Relucenti M, et al. New insights into intestinal permeability in irritable bowel syndrome-like disorders: histological and ultrastructural findings of duodenal biopsies. *Cells* 2021; **10:** 2593.

120 Sapone A, Lammers KM, Mazzarella G, et al. Differential mucosal IL-17 expression in two gliadin-induced disorders: gluten sensitivity and the autoimmune enteropathy celiac disease. *Int Arch Allergy Immunol* 2010; **152:** 75–80.

121 Sapone A, Lammers KM, Casolaro V, et al. Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. *BMC Med* 2011; **9:** 23.

122 Ponzo V, Ferrocino I, Goitre I, et al. Non-celiac gluten/wheat sensitivity: clinical characteristics and microbiota and mycobiota composition by response to the gluten challenge test. *Nutrients* 2021; **13:** 1260.

123 Haro C, Villatoro M, Vaquero L, et al. The dietary intervention of transgenic low-gliadin wheat bread in patients with non-celiac gluten sensitivity (NCGS) showed no differences with gluten free diet (GFD) but provides better gut microbiota profile. *Nutrients* 2018; **10:** 1964.

124 Nylund L, Hakkola S, Lahti L, et al. Diet, perceived intestinal well-being and compositions of fecal microbiota and short chain fatty acids in oat-using subjects with celiac disease or gluten sensitivity. *Nutrients* 2020; **12:** 2570.

125 Nobel YR, Rozenberg F, Park H, et al. Lack of effect of gluten challenge on fecal microbiome in patients with celiac disease and non-celiac gluten sensitivity. *Clin Transl Gastroenterol* 2021; **12:** e00441.

126 Germone M, Wright CD, Kimmons R, Coburn SS. Twitter trends for celiac disease and the gluten-free diet: cross-sectional descriptive analysis. *JMIR Infodemiology* 2022; **2:** e37924.

127 Wu J, Masuy I, Biesiekierski JR, et al. Gut-brain axis dysfunction underlies FODMAP-induced symptom generation in irritable bowel syndrome. *Aliment Pharmacol Ther* 2022; **55:** 670–82.

128 Catassi G, Lener E, Grattagliano MM, et al. The role of microbiome in the development of gluten-related disorders. *Best Pract Res Clin Gastroenterol* 2024; **72:** 101951.

129 Francavilla R, Cristofori F, Verzillo L, et al. Randomized double-blind placebo-controlled crossover trial for the diagnosis of non-celiac gluten sensitivity in children. *Am J Gastroenterol* 2018; **113:** 421–30.