

## REVIEW ARTICLE

## Gluten-related disorders and brain–heart interactions: Pathophysiological links, clinical manifestations, and translational implications

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**Abstract**

Gluten-related disorders (GRDs), including celiac disease, non-celiac gluten sensitivity, and wheat allergy, are increasingly recognized as systemic immune-mediated conditions with clinically significant neurological, psychiatric, and cardiovascular manifestations that extend beyond their classical gastrointestinal phenotype. Epidemiological and clinical evidence have linked GRDs to gluten ataxia, peripheral neuropathy, cognitive dysfunction, affective disorders, increased cardiovascular risk, and autonomic dysregulation. Mechanistic research implicates convergent pathways involving intestinal barrier disruption, systemic immune activation, autoantibody cross-reactivity, blood–brain barrier dysfunction, and endothelial injury mediated by chronic inflammation. This narrative review synthesizes current evidence on the pathophysiology of brain–heart involvement in GRDs through the lens of the gut–brain–heart axis, integrating neuroimmune, autonomic, and vascular mechanisms. We examine the potential for reversibility of selected neurocardiac manifestations through dietary and adjunctive interventions, alongside critical knowledge gaps in mechanistic understanding, biomarker development, and therapeutic targeting. A systems-level framework for understanding GRDs may improve diagnostic recognition, cardiovascular and neurological risk stratification, and inform more integrated clinical management strategies.

**Keywords:** Gluten-related disorders; Celiac disease; Gut–brain–heart axis; Neuroimmune interactions; Autonomic dysfunction; Cardiovascular involvement; Blood–brain barrier dysfunction

## 1. Introduction

Gluten-related disorders (GRDs) comprise a spectrum of conditions triggered by exposure to gluten or wheat proteins and have traditionally been regarded as disorders confined to the gastrointestinal tract, with small-intestinal mucosal injury and resultant malabsorption representing their defining pathological features.<sup>1</sup> However, celiac disease, the most extensively studied GRD, is now recognized as a multisystem immune-mediated disorder with significant extra-intestinal involvement, including neurologic and psychiatric manifestations such as ataxia, neuropathy, and cognitive dysfunction, as well as systemic features that extend beyond the gut.<sup>2</sup> The global prevalence of celiac disease is estimated at approximately 1% of the population, though significant geographic and ethnic variation exists, with many cases remaining undiagnosed due to atypical or subclinical presentations.<sup>3</sup> Epidemiological data indicate a female predominance, with female-to-male ratios of approximately 2–2.5:1, although males tend to present at older ages and more frequently with reduced bone density and lower body mass index. Notably, race- and ethnicity-specific prevalence data remain limited, owing to the predominance of studies conducted in Caucasian populations.<sup>4</sup> Extra-intestinal manifestations have been documented across dermatologic, endocrinologic, hepatic, musculoskeletal, and hematologic systems, underscoring the systemic impact of the disease.<sup>5</sup>

The spectrum of GRDs also includes non-celiac gluten sensitivity (NCGS) and wheat allergy. While the immunopathogenesis of these entities differs from that of celiac disease, evidence supports their capacity to induce systemic symptoms, including neurological complaints and neuropsychiatric features that may improve following gluten exclusion.<sup>6</sup> This broader phenotypic variability has challenged the traditional organ-centric view and has prompted a systems-based perspective. Advances in neuroimmunology and cardiovascular immunology have led to the conceptual framework of the gut–brain–heart axis, defined as an integrated, bidirectional communication network linking the gastrointestinal tract, the central and peripheral nervous systems, immune signaling pathways, and cardiovascular regulation.<sup>7</sup> This axis operates through four principal mechanistic channels:

- (i) Autonomic pathways, through which vagal afferent signaling conveys gut immune status to brainstem centers that regulate cardiac function.
- (ii) Inflammatory pathways, whereby intestinal-derived cytokines and microbial products access the systemic circulation and modulate neural and cardiovascular tissues.
- (iii) Vascular and endothelial pathways, in which chronic

inflammation promotes endothelial dysfunction and oxidative stress.

- (iv) Prothrombotic states affecting cerebrovascular and coronary circulation, and autoantibody-mediated pathways, in which circulating autoantibodies may cross-react with tissue transglutaminase or other antigens expressed in neural and cardiac tissues.<sup>8</sup>

Within this framework, immune signals originating in the gastrointestinal tract may influence central autonomic circuits, vascular function, and cardiomyocyte signaling through these complementary and often overlapping mechanisms, providing a mechanistic substrate for the neurologic and cardiovascular manifestations observed in GRDs.<sup>9</sup>

Against this background, the present narrative review aims to critically examine the influence of GRDs on brain and heart function, integrating mechanistic, clinical, and translational evidence. While previous reviews have comprehensively addressed neurological manifestations of celiac disease or cardiovascular epidemiology in isolation, this work is distinguished by its explicit focus on the brain–heart axis as an integrated pathophysiological unit, emphasizing the role of autonomic dysregulation as a mechanistic bridge between neurological and cardiovascular involvement. Additionally, this review synthesizes emerging evidence on blood–brain barrier (BBB) dysfunction, neurovisceral integration, and the inflammatory reflex—concepts that have not been systematically applied to GRDs despite their established relevance in other immune-mediated conditions. By adopting a brain–heart systems perspective, this work aims to move beyond compartmentalized symptom descriptions and provide a coherent framework for understanding gluten-driven multisystem pathology, with direct implications for risk stratification, biomarker development, and integrated clinical management.

## 2. Methods

This narrative review was conducted and reported in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA), a validated instrument developed to improve the transparency, methodological rigor, and scientific quality of narrative syntheses in biomedical research.<sup>10</sup> The SANRA framework was adopted prospectively to guide the conceptualization, literature selection, and synthesis process, with explicit attention to its six core domains:

- (i) Justification of the narrative review format.
- (ii) Clarity of objectives.
- (iii) Adequacy of the literature search.
- (iv) Appropriateness and consistency of referencing.

- (v) Scientific reasoning.
- (vi) Balanced presentation of evidence.

A structured but flexible literature search strategy was applied to identify peer-reviewed publications addressing the neurological and cardiovascular implications of GRDs, including celiac disease, NCGS, and wheat allergy. Searches were conducted using MEDLINE/PubMed, Scopus, and Web of Science through December 2025, with priority given to studies published within the past 10 years to capture contemporary understanding of brain–heart interactions in GRDs.

The search strategy employed a combination of controlled vocabulary and free-text terms. In MEDLINE/PubMed, Medical Subject Headings terms included “Celiac Disease,” “Peripheral Nervous System Diseases,” “Central Nervous System Diseases,” “Cardiovascular Diseases,” “Autonomic Nervous System,” “Arrhythmias, Cardiac,” and “Blood–Brain Barrier.” These were combined with free-text keywords using Boolean operators. Example search strings included: (“celiac disease” OR “coeliac disease” OR “gluten sensitivity” OR “non-celiac gluten sensitivity” OR “NCGS” OR “wheat allergy”) AND (neurolog\* OR neuropath\* OR ataxia OR cognit\* OR psychiatr\* OR depress\* OR anxiety OR “brain fog” OR cardiovasc\* OR cardiac OR arrhythm\* OR “heart rate variability” OR “autonomic dysfunction” OR “orthostatic intolerance” OR endotheli\* OR inflamm\* OR “gut–brain axis” OR “gut–brain–heart axis” OR “blood–brain barrier”). Similar strategies were adapted for Scopus and Web of Science using their respective controlled vocabularies and wildcard conventions.

To ensure conceptual completeness, reference lists of key articles and authoritative reviews were manually screened by two authors (YVT and PVP) to identify additional relevant publications not captured by the primary search. Study selection was conducted in two stages. First, titles and abstracts were screened for relevance based on the inclusion criteria. Studies were retained if they addressed at least one GRD (celiac disease, NCGS, or wheat allergy) and at least one neurological, cardiovascular, or autonomic outcome. Second, full-text articles of potentially relevant studies were retrieved and assessed for eligibility. Disagreements regarding study inclusion were resolved through discussion and, when necessary, consultation with a third reviewer (GV) to reach a consensus.

Given the narrative format of this review, formal risk-of-bias assessment tools were not applied; however, methodological quality was evaluated narratively based on study design (prioritizing prospective cohorts, randomized controlled trials, and mechanistic studies with appropriate controls), sample size, diagnostic validation of GRDs, standardization of outcome measures, and transparency

of reporting. Studies with unclear diagnostic criteria, small convenience samples without adequate characterization, or a lack of peer review were considered lower quality and interpreted with appropriate caution. This quality appraisal informed the interpretative weight assigned to individual studies during synthesis, with mechanistic convergence across multiple independent lines of evidence (e.g., clinical observation, epidemiology, translational models, and pathophysiological plausibility) strengthening confidence in reported associations.

Eligible sources included original clinical studies, epidemiological investigations, translational and mechanistic research, consensus documents, and high-quality narrative or systematic reviews published in English. *In vivo* and *in vitro* studies were considered selectively when they provided mechanistic insight directly relevant to human pathophysiology. Editorials, opinion pieces, and non-peer-reviewed sources were excluded. Study selection emphasized relevance, methodological robustness, and contribution to mechanistic or clinical understanding rather than formal evidence hierarchies, consistent with the exploratory aims of a SANRA-guided narrative review.

Data extraction focused on five thematic domains: (i) “immunopathophysiology of GRDs,” (ii) “central nervous system involvement in GRDs,” (iii) “cardiovascular involvement in GRDs,” (iv) “the gut–brain–heart axis in GRDs,” and (v) “therapeutic implications and reversibility of brain–heart effects.” Evidence was synthesized qualitatively using a thematic, systems-based approach, highlighting areas of convergence, divergence, and uncertainty across disease entities (Table 1).

In synthesizing evidence, mechanistic studies were used to establish biological plausibility and to identify pathways linking gluten exposure to neurocardiac outcomes, while clinical and epidemiological studies provided evidence of the occurrence, prevalence, and clinical significance of these manifestations in patient populations. Mechanistic evidence was weighted based on reproducibility, translational relevance to human physiology, and concordance with clinical observations. When mechanistic and clinical evidence converged, for example, when intestinal barrier dysfunction (mechanistic) was linked to documented neurological outcomes in well-characterized celiac cohorts (clinical), confidence in the proposed pathway was deemed higher. Conversely, when clinical associations were observed without clear mechanistic support, or when mechanistic data were derived solely from *in vitro* systems without clinical validation, findings were presented with appropriate interpretive caution. Conflicting findings were explicitly acknowledged to minimize interpretative bias, and areas

Table 1. Summary of included studies

| Topics                                                            | Sub-topics                                                                                                                                                    | Results                                                                                                                                                                                                                                                        |
|-------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Immunopathophysiology of gluten-related disorders                 | (i) Adaptive and innate immune activation<br>(ii) Intestinal barrier dysfunction and systemic immune signaling                                                | Celiac disease: Autoimmune gluten response affecting gut, nerves, and heart<br>Nonceliac gluten sensitivity/wheat allergy: Innate immune or immunoglobulin E-mediated pathways producing lowgrade systemic inflammation                                        |
| Central nervous system involvement in gluten-related disorders    | (i) Neurological manifestations<br>(ii) Psychiatric and affective dimensions<br>(iii) Blood–brain barrier dysfunction and neuroimmune interactions            | Gluten-induced autoimmunity can cause cerebellar ataxia, peripheral neuropathy, epilepsy, headaches, and cognitive/psychiatric symptoms through blood–brain barrier disruption and antitissue transglutaminase antibodies, even without gut disease            |
| Cardiovascular involvement in gluten-related disorders            | (i) Epidemiological associations<br>(ii) Inflammation, endothelial dysfunction, and thrombosis<br>(iii) Autonomic dysregulation and cardiac electrophysiology | Studies link celiac disease to higher ischemic heart disease, atrial fibrillation, and stroke risk, independent of traditional factors, likely via inflammation, endothelial dysfunction, and autonomic dysregulation; non-celiac evidence remains preliminary |
| The gut–brain–heart axis in gluten-related disorders              | -                                                                                                                                                             | The gut–brain–heart axis describes bidirectional immune and neural communication from gut inflammation to brain and heart, influencing autonomic control and symptoms like fatigue and palpitations                                                            |
| Therapeutic implications and reversibility of brain–heart effects | -                                                                                                                                                             | A gluten-free diet is the main therapy; adherence restores the barrier and reduces inflammation and extra-intestinal symptoms; however, some patients need adjunctive measures                                                                                 |

of ongoing scientific debate, particularly regarding NCGS, were identified and discussed transparently.

### 3. Results

#### 3.1. Immunopathophysiology of gluten-related disorders

##### 3.1.1. Mechanisms of immune activation in gluten-related disorders

(a) Celiac disease: Human leukocyte antigen-restricted adaptive immunity and autoimmunity

Celiac disease represents the prototypical autoimmune form of GRD and is characterized by a highly specific human leukocyte antigen (HLA)-DQ2/DQ8–restricted adaptive immune response to dietary gluten in genetically predisposed individuals. Susceptibility is strongly associated with the expression of HLA-DQ2 (carried by approximately 90–95% of celiac patients) and/or HLA-DQ8 (most remaining cases), though these alleles are necessary but not sufficient for disease development, as they are also present in approximately 30–40% of the general population.<sup>11</sup>

The pathogenic cascade is initiated when gliadin peptides, which are resistant to complete degradation by gastric and pancreatic proteases, cross the intestinal epithelium and encounter tissue transglutaminase 2 (TG2) in the lamina propria. TG2 selectively deamidates

glutamine residues within gliadin peptides to glutamic acid, thereby creating negatively charged residues that dramatically increase peptide affinity for the HLA-DQ2/DQ8 binding groove.<sup>12</sup> This post-translational modification enables highly efficient presentation of gliadin epitopes to CD4<sup>+</sup> T cells, triggering robust T-cell activation and clonal expansion. The resultant adaptive immune response is characterized by a Th1-skewed cytokine profile dominated by interferon- $\gamma$  production, which drives inflammatory tissue remodeling, including crypt hyperplasia, villous atrophy, and intraepithelial lymphocytosis—the histological hallmarks of celiac disease (Figure 1).<sup>12</sup>

Critically, TG2 itself becomes a target of the adaptive immune response, with anti-TG2 immunoglobulin (Ig) A antibodies serving as the principal serological biomarker of active disease. Although the small intestine is the primary site of injury, celiac disease is now recognized as a systemic immune-mediated disorder. Activated gluten-specific T cells, pro-inflammatory cytokines, and circulating autoantibodies—including anti-tissue transglutaminase antibodies—can disseminate systemically and interact with extra-intestinal tissues.<sup>13</sup> Given the widespread expression of tissue transglutaminase in the nervous system, myocardium, and vascular endothelium, autoimmune cross-reactivity provides a biologically plausible mechanism for neurological and cardiovascular involvement.

(b) Non-celiac gluten sensitivity: Innate immune activation and epithelial stress

Non-celiac gluten sensitivity is defined by the absence of the pathognomonic features of celiac disease, specifically, negative celiac-specific serology (anti-TG2, anti-endomysial, anti-deamidated gliadin peptide antibodies), absence of villous atrophy on small bowel biopsy, and lack of HLA-DQ2/DQ8 restriction, yet is characterized by reproducible symptomatic responses to gluten ingestion that improve with gluten withdrawal.<sup>14</sup> The biological basis of NCGS remains under active investigation, with ongoing scientific debate regarding the relative contributions of gluten versus other wheat components (e.g., amylase-trypsin inhibitors and fermentable oligosaccharides) to symptom generation.<sup>15</sup>

Current mechanistic models emphasize a predominant role for innate immune activation rather than adaptive autoimmunity. Proposed pathways include activation of pattern recognition receptors (e.g., Toll-like receptors), epithelial stress responses, altered expression of tight junction proteins (with resultant increased intestinal permeability), and low-grade mucosal inflammation characterized by increased intraepithelial lymphocytes in the absence of architectural distortion.<sup>14</sup> These innate immune responses are hypothesized to generate transient, low-grade systemic inflammation capable of producing extra-intestinal neurological and systemic symptoms despite preserved villous architecture. However, diagnostic criteria for NCGS remain under refinement, standardized biomarkers are lacking, and the degree to which symptoms reflect immune activation, metabolic responses, or other mechanisms continues to be debated within the scientific community.<sup>16</sup>

(c) Wheat allergy: Immunoglobulin E-mediated hypersensitivity

Wheat allergy represents a mechanistically distinct entity within the spectrum of GRDs, fundamentally differing from celiac disease and NCGS in both its immune pathway and clinical time course. Wheat allergy is mediated by classical IgE-dependent type I hypersensitivity reactions. Following sensitization, re-exposure to wheat allergens—including specific wheat proteins such as  $\omega$ -5 gliadin, lipid transfer proteins, and other immunogenic components—triggers the cross-linking of allergen-specific IgE antibodies bound to high-affinity Fc $\epsilon$ RI receptors on mast cells and basophils.<sup>17</sup> This cross-linking induces rapid degranulation with release of preformed inflammatory mediators, including histamine, tryptase, and leukotrienes, as well as de novo synthesis of prostaglandins and cytokines. The resultant systemic effects occur within minutes to hours of wheat exposure and may produce acute gastrointestinal

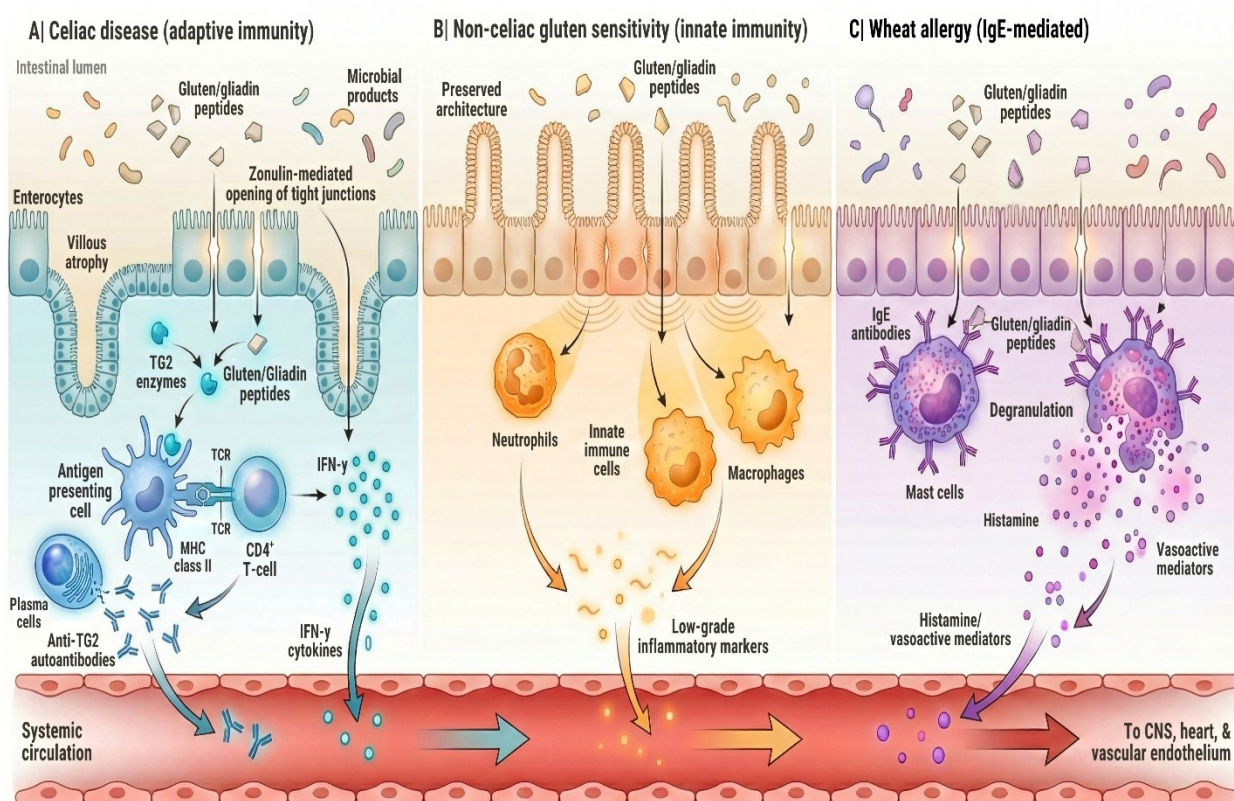
symptoms (e.g., nausea, vomiting, abdominal pain), respiratory manifestations (e.g., bronchospasm, rhinitis), cutaneous reactions (e.g., urticaria, angioedema), and in severe cases, cardiovascular collapse (e.g., anaphylaxis) (Figure 1).<sup>17</sup> Importantly, these manifestations reflect acute, transient neurovascular and hemodynamic effects mediated by vasoactive substances, rather than the chronic, immune-mediated tissue injury and architectural remodeling characteristic of celiac disease. Wheat allergy is typically diagnosed by demonstration of wheat-specific IgE antibodies in serum or by skin prick testing and management centers on strict wheat avoidance.<sup>18</sup>

### 3.1.2. Intestinal barrier dysfunction and systemic immune signaling

Despite their distinct immunopathogenic mechanisms, a unifying pathophysiological feature across all three GRD categories is altered intestinal barrier integrity, representing a convergent pathway through which mechanistically disparate processes can produce shared systemic consequences. Disruption of tight-junction regulation increases paracellular permeability, facilitating the translocation of gluten peptides, microbial products, and inflammatory mediators into the systemic circulation (Figure 1). The regulation of intestinal permeability through zonulin-dependent mechanisms has been proposed as a key link between gluten exposure, immune activation, and extra-intestinal disease vulnerability.<sup>19</sup> Systemic dissemination of these immune signals provides a mechanistic substrate for distant organ involvement, including effects on the central nervous system and the cardiovascular system.

Given the complex immunopathogenesis of GRDs, several non-dietary therapeutic strategies targeting key molecular activation pathways are under clinical investigation, though none have yet received regulatory approval for routine use. Investigational approaches include tight junction regulators (e.g., larazotide acetate, a zonulin antagonist designed to restore intestinal barrier function), gluten-degrading enzymes intended to reduce immunogenic peptide exposure in the gut lumen, and peptide-based vaccines aimed at inducing immune tolerance to gluten epitopes.<sup>20-22</sup>

Early-phase clinical trials have shown modest efficacy in reducing gastrointestinal symptoms in selected patients with celiac disease, but effects on extra-intestinal manifestations—including neurological and cardiovascular outcomes—remain unexplored, and long-term safety and efficacy data are lacking.<sup>20</sup> As such, the gluten-free diet remains the only evidence-based disease-modifying intervention, though adjunctive



**Figure 1.** Comparative immunopathophysiology and systemic dissemination in gluten-related disorders. (A) In celiac disease, TG2 deamidates gliadin peptides, enabling HLA-DQ2/DQ8-mediated Th1 activation and antiTG2 autoantibody production, culminating in smallintestinal villous atrophy. (B) Nonceliac gluten sensitivity preserves villous architecture; innate immune activation and epithelial stress generate lowgrade inflammation and diverse extraintestinal symptoms. (C) Wheat allergy is an IgE-mediated hypersensitivity in which allergenspecific IgE is crosslinked on mast cells, releasing histamine and cytokines that cause acute reactions. Across these conditions, increased intestinal permeability may allow luminal antigens and inflammatory mediators into circulation, potentially affecting distant organs, including the brain and heart. Image created using GPAI Pro and BioRender.com.

Abbreviations: CD: Cluster of differentiation; CNS: Central nervous system; HLA: Human leukocyte antigen; IFN: Interferon; IgE: Immunoglobulin E; MHC: Major histocompatibility complex; TG2: Tissue transglutaminase 2; TCR: T-cell receptor; TCR: T-cell receptor.

pharmacotherapy represents a promising area of ongoing translational research.

### 3.2. Central nervous system involvement in gluten-related disorders

#### 3.2.1. Neurological manifestations

Central nervous system involvement represents one of the most clinically significant extra-intestinal dimensions of GRDs.<sup>2</sup> In celiac disease, neurological manifestations are well documented and include cerebellar ataxia, peripheral neuropathy, epilepsy, headache syndromes, and varying degrees of cognitive impairment.<sup>2</sup> The reported prevalence of neurological complications in celiac disease varies substantially based on study setting and case ascertainment methods. Population-based cohort studies report neurological manifestations in approximately

6–10% of individuals with biopsy-confirmed celiac disease<sup>23,24</sup>, whereas specialty neurology clinic-based series report higher rates (up to 40–50%), reflecting referral bias and selective evaluation of patients with prominent neurological symptoms.<sup>25</sup>

Among documented manifestations, peripheral neuropathy is the most common neurological complication in both population-based and clinic-based studies, followed by ataxia and seizure disorders, although the strength of association varies across outcomes (Figure 2). Importantly, these manifestations may occur independently of gastrointestinal symptoms, contributing to delayed diagnosis and under-recognition of the neurological phenotype of the disease.<sup>25</sup> The prevalence and diversity of these manifestations support the concept that celiac disease should be regarded as a systemic disorder

with direct neurological relevance, rather than a purely intestinal condition.<sup>26</sup> The strength of association between celiac disease and specific neurological manifestations varies across outcomes, with corresponding differences in the quality and consistency of supporting evidence.

Gluten ataxia represents the most robustly established neurological complication, supported by case-control studies demonstrating cerebellar antibodies in affected patients, neuropathological evidence of Purkinje cell loss, and prospective data showing stabilization or improvement with gluten-free diet in early-stage disease.<sup>26</sup>

Peripheral neuropathy, while highly prevalent, shows a weaker and more heterogeneous association: large population-based cohort studies confirm increased risk compared to matched controls, but the attributable fraction is modest, and many cases occur in the context of other risk factors (e.g., diabetes, alcohol use, vitamin deficiencies), thereby complicating causal inference.<sup>23,24</sup> The association between celiac disease and epilepsy is supported primarily by registry-based studies showing moderately increased prevalence, though whether this reflects shared genetic susceptibility, secondary effects of nutritional deficiency, or direct immune-mediated mechanisms remains debated.<sup>25</sup>

For headache and migraine, evidence derives largely from cross-sectional surveys and clinic-based case series, with inconsistent findings across studies and limited prospective validation, suggesting a possible but not definitively established association that may be confounded by reporting bias and healthcare-seeking behavior. Cognitive impairment, particularly subjective complaints of “brain fog,” is frequently reported in both celiac disease and NCGS. However, objective neuropsychological testing yields variable and often subtle deficits, and population-based studies do not consistently demonstrate elevated rates of dementia or measurable cognitive decline, indicating that while subjective cognitive symptoms are common, their neurobiological substrate and clinical significance remain incompletely characterized.<sup>27</sup>

These symptoms are particularly prominent in NCGS, although it is important to note that evidence for neurological involvement in NCGS derives almost entirely from self-reported symptom questionnaires and uncontrolled case series rather than population-based studies with validated neurological assessments. Objective correlates on conventional neuroimaging are typically absent, and controlled provocation studies with blinded gluten challenge yield inconsistent results regarding the reproducibility of neurological symptoms.

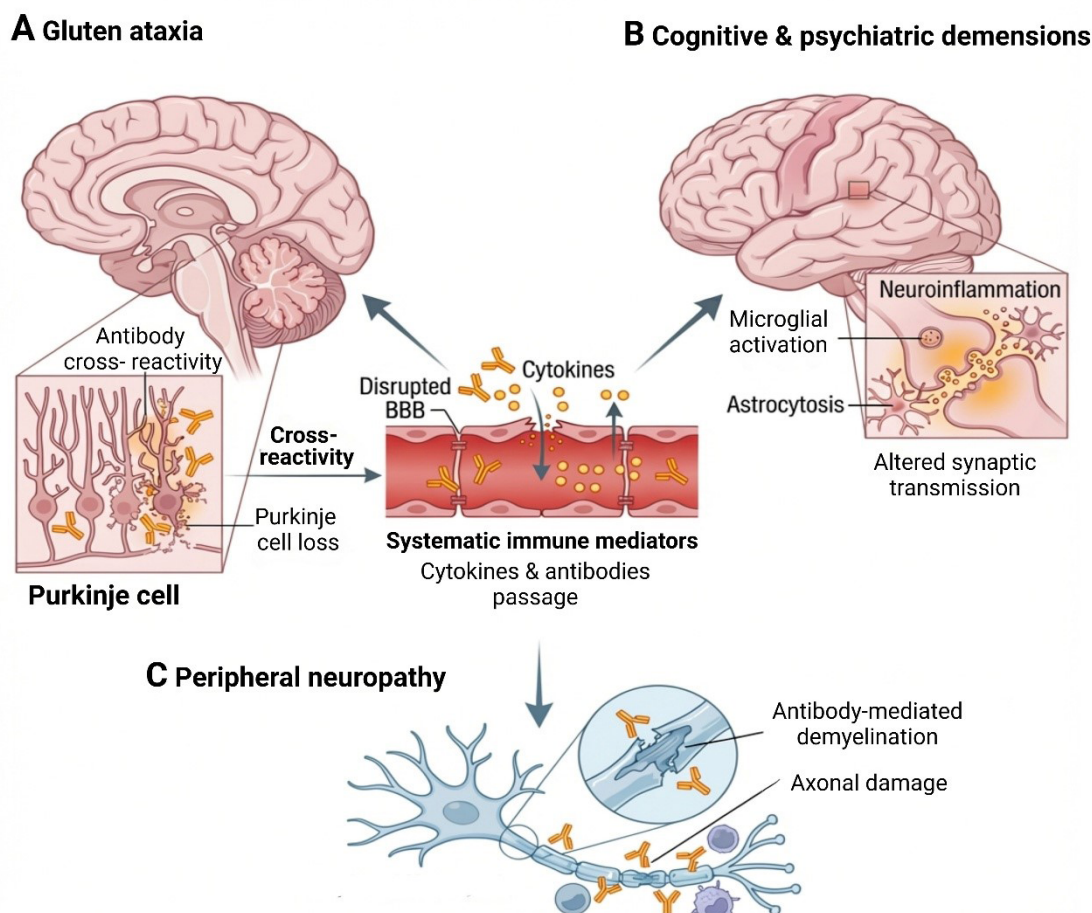
### **3.2.2. Psychiatric and affective dimensions**

Psychiatric manifestations are increasingly recognized as integral components of the GRD phenotype. The strength of association between celiac disease and psychiatric outcomes varies by disorder type and is influenced by study methodology. Large registry-based cohort studies have demonstrated a modest but statistically significant increase in depression and anxiety disorders in individuals with celiac disease compared to matched population controls, with hazard ratios typically in the range of 1.3–1.8, suggesting a real but moderate elevation in risk.<sup>28</sup> These associations are most robust when psychiatric diagnoses are ascertained through clinical registries or prescription records, reducing recall bias inherent in self-reported measures.

However, distinguishing primary biological mechanisms from secondary psychosocial contributors remains challenging. While psychosocial factors related to chronic illness, dietary restriction, social limitations, and diagnostic burden undoubtedly contribute, biological mechanisms linking systemic immune activation to affective dysregulation are increasingly emphasized. Systemic inflammation can influence central neurotransmission, neuroendocrine stress responses, and emotional regulation, thereby providing a plausible mechanistic bridge between gluten-driven immune activity and psychiatric symptoms (Figure 2). Importantly, improvement of neuropsychiatric symptoms has been observed in a subset of patients following strict gluten withdrawal, supporting a contributory role of gluten-related immune mechanisms rather than a purely reactive or psychosomatic explanation.<sup>28</sup>

### **3.2.3. Blood–brain barrier dysfunction and neuroimmune interactions**

A critical link between peripheral immune activation and central nervous system involvement is the integrity of the BBB. Systemic inflammation associated with gluten-related immune responses may compromise barrier function, facilitating the entry of cytokines, immune complexes, and autoantibodies into the central nervous system (Figure 2).<sup>29</sup> However, direct evidence for BBB dysfunction in celiac disease is limited and derives primarily from mechanistic studies in animal models and small case series in humans with severe neurological complications.<sup>30</sup> The detection of anti-tissue transglutaminase or other gluten-related antibodies in cerebrospinal fluid has been reported in selected patients with gluten ataxia and other neurological manifestations, supporting the concept of direct immune-



**Figure 2.** Pathophysiology of gluten-related neurological disorders. Disruption of the blood–brain barrier by gluten allows cytokines and antibodies to enter neural tissues. (A) Gluten ataxia: Purkinje cell loss due to antibody crossreactivity. (B) Cognitive and psychiatric effects: Neuroinflammation with microglial and astrocytic activation, impairing synaptic function. (C) Peripheral neuropathy: Immune-mediated demyelination and axonal damage in peripheral nerves. Image created using GPAI Pro and BioRender.com.

mediated neural injury. However, these findings have not been consistently replicated, and their prevalence in the broader celiac population remains uncertain.<sup>29</sup> These observations highlight the potential role of neuroimmune interactions in disease expression, particularly in patients with overt neurological syndromes, while acknowledging that the generalizability of these mechanisms to milder or subclinical neurological involvement requires further population-based validation.

### 3.3. Cardiovascular involvement in gluten-related disorders

#### 3.3.1. Epidemiological associations

Increasing epidemiological evidence supports an association between celiac disease and adverse cardiovascular outcomes.<sup>31</sup> Large population-based cohort studies have demonstrated a higher incidence of ischemic

heart disease, atrial fibrillation, and cerebrovascular events in individuals with celiac disease compared with the general population.<sup>32</sup> Importantly, this excess risk appears to be most pronounced in the period surrounding diagnosis, suggesting that active, untreated disease and systemic inflammation may play a critical role.

A nationwide cohort study based on biopsy-verified celiac disease reported a significantly increased risk of ischemic heart disease, independent of traditional cardiovascular risk factors.<sup>33</sup> Subsequent population-based analyses have also identified an increased risk of atrial fibrillation in celiac disease, reinforcing the link between chronic immune-mediated inflammation and arrhythmogenic vulnerability.<sup>34</sup> While malabsorption-related deficiencies (e.g., iron, folate, and vitamin B12) may contribute to endothelial dysfunction and hyperhomocysteinemia, these factors do not fully account

for the observed cardiovascular risk, which persists after multivariable adjustment. In contrast, NCGS and wheat allergy remain underrepresented in cardiovascular epidemiology. Available data are sparse and largely observational, but clinical reports describe autonomic symptoms, palpitations, and orthostatic intolerance in selected patients. At present, these findings should be regarded as hypothesis-generating rather than conclusive.

### 3.3.2. Inflammation, endothelial dysfunction, and thrombosis

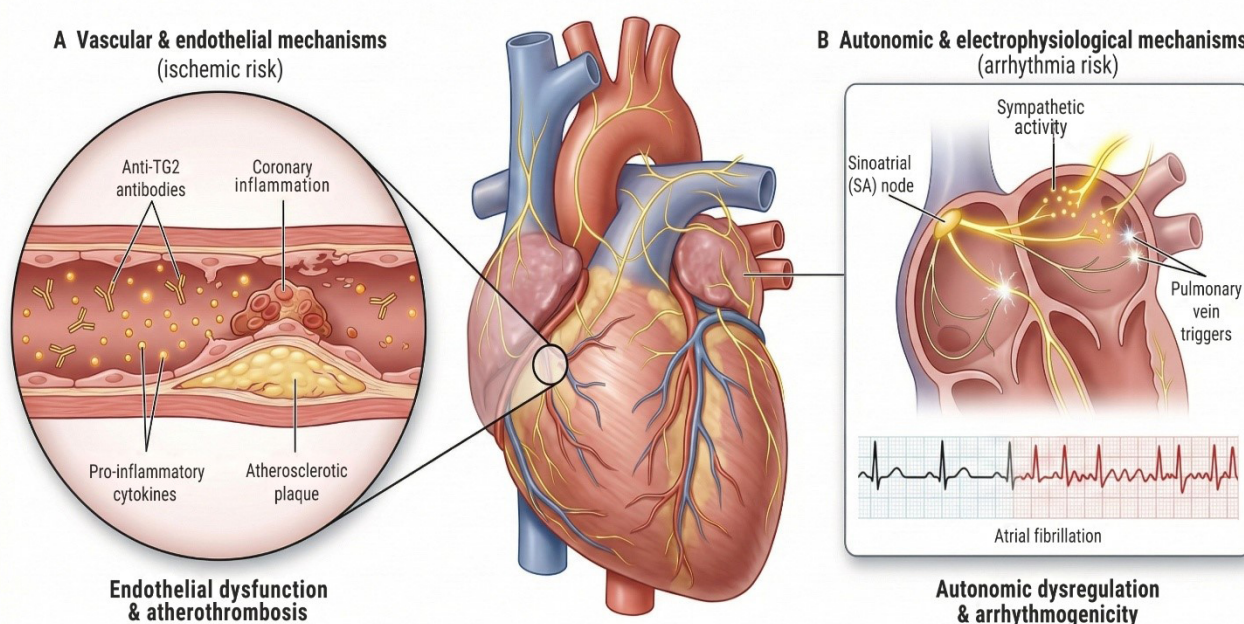
From a mechanistic standpoint, chronic low-grade systemic inflammation provides a plausible link between gluten-related immune activation and cardiovascular disease.<sup>2</sup> Untreated celiac disease is characterized by circulating pro-inflammatory cytokines and immune mediators that may impair endothelial nitric oxide signaling, promote oxidative stress, and accelerate atherosclerotic processes (Figure 3).<sup>35</sup> Inflammatory activation of coagulation pathways may further contribute to a prothrombotic milieu, potentially explaining the increased incidence of ischemic events observed in epidemiological studies.

Furthermore, malabsorption-related micronutrient deficiencies, particularly folate, vitamin B12, and vitamin B6, contribute to elevated homocysteine levels, an

independent risk factor for endothelial dysfunction and atherothrombosis documented in untreated celiac disease patients.<sup>36</sup> Autoimmune mechanisms may also contribute. Tissue transglutaminase—the primary autoantigen in celiac disease—is expressed in vascular endothelial cells, raising the possibility that circulating anti-transglutaminase antibodies interact with the vascular wall and influence endothelial integrity.<sup>35</sup> Although direct causal evidence remains limited, this hypothesis aligns with broader concepts linking autoimmunity and vascular dysfunction.

### 3.3.3. Autonomic nervous system dysregulation and cardiac electrophysiology

Autonomic nervous system dysfunction represents a critical interface between neurological and cardiovascular involvement in GRDs. Reduced heart rate variability, orthostatic intolerance, and features of dysautonomia have been described in patients with celiac disease, particularly in those with neurological manifestations (Figure 3).<sup>37</sup> Such alterations may reflect impaired central autonomic regulation or persistent inflammatory signaling. Quantitative assessments have demonstrated significantly reduced vagal modulation indices and time-domain heart rate variability parameters in celiac patients compared to healthy controls, with some studies reporting partial normalization following gluten-free diet adherence.<sup>38</sup>



**Figure 3.** Pathophysiological pathways linking gluten-related disorders to cardiovascular risk. This schematic delineates two interrelated pathophysiologic pathways that may underlie adverse cardiovascular sequelae. (A) Chronic inflammation and antitissue transglutaminase 2 (TG2) antibodies damage the endothelium, causing oxidative stress, accelerated atherosclerosis, and prothrombotic states that increase the risk of ischemic heart disease. (B) Sympathetic dominance with reduced vagal tone alters sinoatrial node and pulmonary vein innervation, promoting arrhythmogenic substrates and increased susceptibility to atrial fibrillation. Image created using GPAI Pro and BioRender.com.

Clinically, autonomic imbalance is relevant not only because it contributes to symptoms such as palpitations, fatigue, and exercise intolerance, but also because reduced parasympathetic tone coupled with sympathetic predominance is a recognized risk factor for atrial fibrillation and adverse cardiovascular outcomes, providing a mechanistic bridge between immune activation and electrophysiological vulnerability.

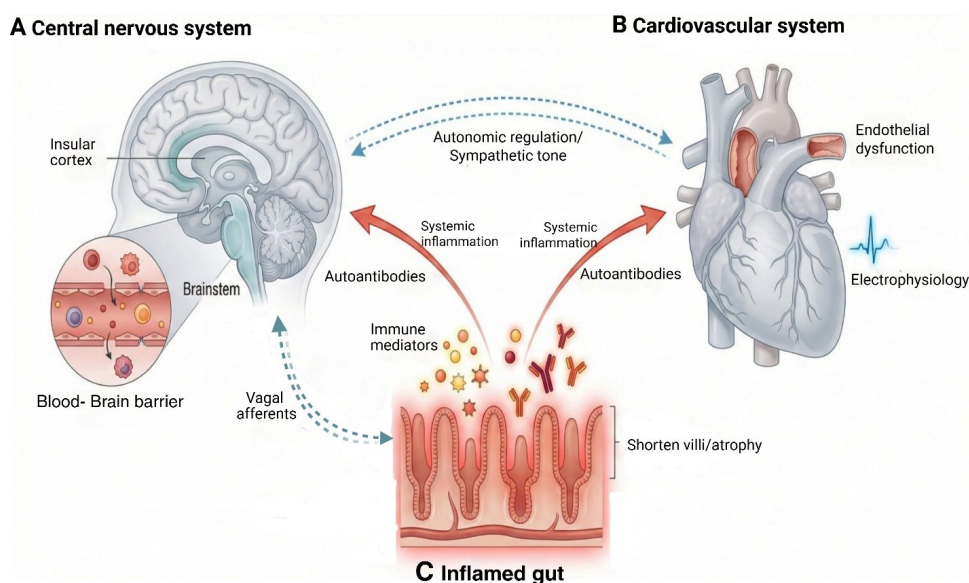
### 3.4. The gut–brain–heart axis in gluten-related disorders

As introduced earlier, the gut–brain–heart axis represents an integrated, bidirectional communication network through which intestinal immune activation and barrier dysfunction can exert distal effects on brain function, autonomic control, and cardiac physiology.<sup>39</sup> In GRDs, persistent or recurrent exposure to gluten represents a chronic immune stimulus capable of perturbing this interconnected system through four principal mechanistic channels: autonomic, inflammatory, vascular/endothelial, and autoantibody-mediated pathways. These channels operate in parallel, interacting synergistically to produce the spectrum of neurocardiac manifestations observed clinically.

The following sections examine each pathway separately before integrating their contributions within a unified

systems-level framework. Within this axis, immune-to-brain signaling occurs through complementary humoral and neural pathways. Pro-inflammatory cytokines generated in the gut can access or signal across the BBB, while vagal afferent fibers convey immune and inflammatory information directly to brainstem nuclei and higher autonomic centers. These mechanisms are well established in the broader context of immune system–brain communication and provide a biologically plausible route through which intestinal inflammation influences central autonomic regulation.<sup>40</sup> Emerging evidence also implicates alterations in gut microbiome composition (dysbiosis) as a key mediator within the gut–brain–heart axis.<sup>41</sup> Celiac disease is associated with reduced microbial diversity, altered *Firmicutes/Bacteroidetes* ratios, and diminished production of short-chain fatty acids, which play regulatory roles in both intestinal barrier integrity and systemic immune modulation.<sup>42</sup>

Central integration of interoceptive and immune signals occurs within the central autonomic network, a distributed set of cortical and subcortical regions that includes the insular cortex, anterior cingulate cortex, hypothalamus, amygdala, and brainstem autonomic nuclei.<sup>43</sup> This network coordinates autonomic, neuroendocrine, and behavioral responses and exerts direct control over heart rate, vascular tone, and cardiac electrophysiology.<sup>44</sup> Importantly,



**Figure 4.** Schematic illustration of the gut–brain–heart axis, showing the integrated immune and neural signaling networks. This schematic summarizes bidirectional pathways through which intestinal pathology may contribute to neurocardiac dysfunction in gluten-related disorders. (A) Gut inflammation releases cytokines and autoantibodies, disrupting the blood–brain barrier and promoting neuroinflammation, endothelial dysfunction, and thrombotic risk. (B) Vagal afferent signaling causes sympathetic predominance and reduced parasympathetic tone. (C) Combined immune–neural effects manifest as fatigue, brain fog, palpitations, orthostatic intolerance, and increased susceptibility to arrhythmia and ischemic heart disease. Image created using GPAI Pro and BioRender.com.

these same regions are involved in pain modulation<sup>45</sup>, fatigue perception, and emotional regulation, providing a neuroanatomical substrate for the co-occurrence of neurological, autonomic, and cardiovascular symptoms observed in some patients with GRDs (Figure 4).

From a cardiovascular perspective, brain–heart coupling is further conceptualized by the neurovisceral integration model, which links central regulatory circuits to cardiac autonomic output and cardiovascular risk.<sup>46</sup> Dysregulation of these circuits is associated with reduced heart rate variability, impaired stress adaptation, and increased vulnerability to arrhythmias.<sup>47</sup> Immune signaling intersects with this system through the inflammatory reflex, a vagus-mediated pathway by which immune activation modulates both central autonomic function and peripheral organ inflammation.<sup>48</sup>

Clinically, disruption of the gut–brain–heart axis provides a coherent explanation for complex symptom constellations reported in GRDs, including cognitive dysfunction, fatigue, palpitations, orthostatic intolerance, and reduced exercise capacity, often in the absence of overt structural disease. Recognizing GRDs as conditions that engage this integrated axis supports a systems-based approach to diagnosis and management, bridging gastroenterology, neurology, and cardiovascular medicine.

Looking forward, emerging approaches hold promise for advancing mechanistic understanding of the gut–brain–heart axis in GRDs. Nanoscale imaging techniques, including atomic force microscopy and tip-enhanced Raman spectroscopy, offer unprecedented spatial resolution to directly visualize molecular processes at the tissue interface—such as tight junction disruption, immune cell–epithelial interactions, and BBB alterations—that are central to GRD pathophysiology but remain incompletely characterized at the submolecular level.<sup>49</sup>

In parallel, integrative multi-omics approaches that combine metagenomics, metabolomics, transcriptomics, and neuroimaging data enable systems-level mapping of microbiota–host interactions and their downstream effects on neural and cardiovascular function.<sup>50</sup> These data-driven strategies have already yielded novel microbial and metabolite signatures linked to neurological outcomes in other immune-mediated and neurodegenerative conditions, providing a translational roadmap for identifying GRD-specific biomarkers and therapeutic targets. Applying these technologies to well-phenotyped GRD cohorts, with longitudinal assessment of gut, brain, and cardiac parameters, represents a critical next step toward deciphering the biomolecular determinants of neurocardiac involvement and informing precision medicine strategies.

### 3.5. Therapeutic implications and reversibility of brain–heart effects

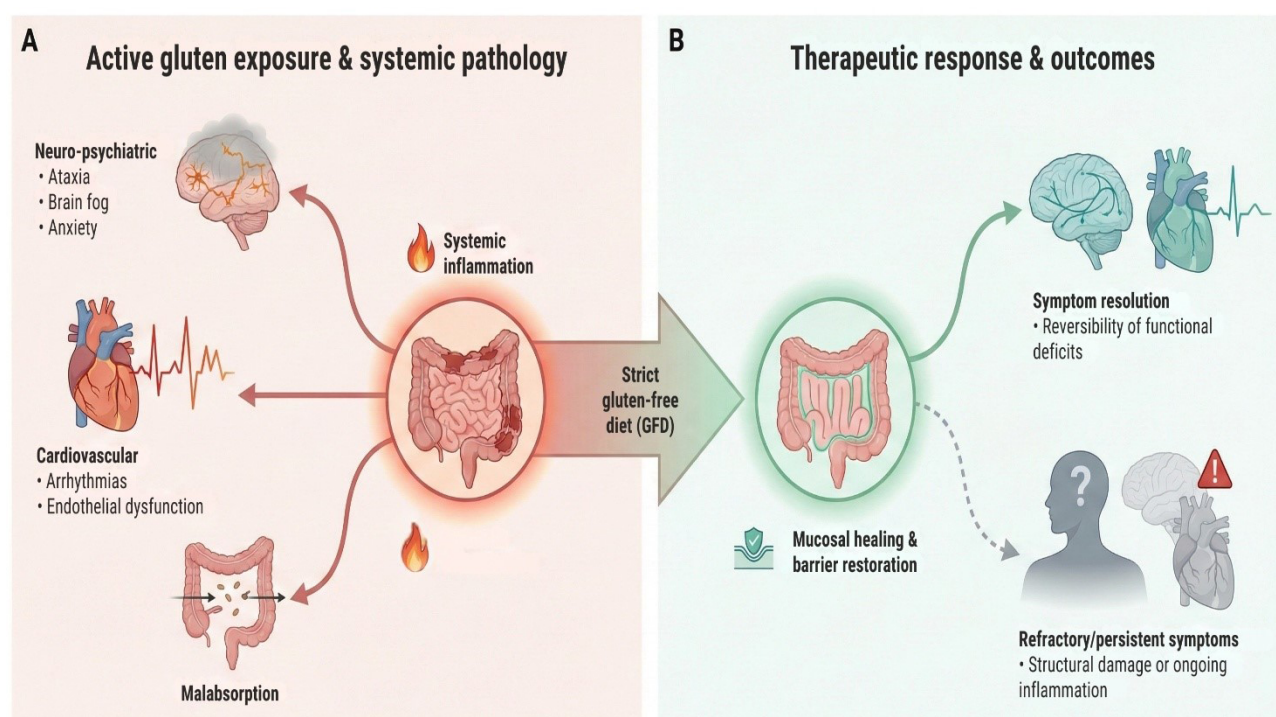
The gluten-free diet (GFD) remains the cornerstone of therapy for celiac disease and is commonly adopted in individuals with NCGS (Figure 5).<sup>51</sup> From a pathophysiological perspective, strict and sustained gluten withdrawal is the only currently available disease-modifying intervention capable of suppressing antigen-driven immune activation, restoring intestinal barrier integrity, and reducing systemic inflammatory signaling. Contemporary clinical guidance emphasizes that early diagnosis and rigorous dietary adherence are essential not only for achieving intestinal mucosal healing, but also for limiting or preventing extra-intestinal complications, including neurological and cardiovascular manifestations.<sup>52</sup> However, strict adherence to a GFD remains challenging, with studies reporting non-adherence rates ranging from 42% to 91% depending on assessment methods, primarily due to inadvertent gluten exposure, social constraints, cost, and palatability concerns.<sup>53,54</sup>

Clinical observations and longitudinal studies indicate that adherence to a GFD may be associated with partial or complete improvement in selected neurological symptoms, affective disturbances, and cardiac complaints, particularly when treatment is initiated early in the disease course.<sup>2,5,55</sup> These findings support the concept that a proportion of brain–heart alterations in GRDs are functionally mediated and potentially reversible, rather than exclusively structural or degenerative. Reduction in systemic inflammation and nutritional status may further contribute to normalization of vascular and autonomic function over time.

Nevertheless, dietary therapy is not universally effective. A substantial subset of patients continues to report persistent cognitive complaints, fatigue, dysautonomia, or cardiovascular symptoms despite strict adherence to a GFD and documented intestinal recovery.<sup>51,56</sup> This dissociation suggests that immune-mediated, neurovascular, or autonomic alterations may become partially self-sustaining or incompletely responsive to gluten exclusion. Current clinical guidelines acknowledge this limitation and highlight the need for careful follow-up and evaluation of ongoing extra-intestinal symptoms.<sup>57</sup> Collectively, these findings underscore the importance of moving beyond a diet-only paradigm in selected patients and support the development of adjunctive strategies targeting residual inflammation, barrier dysfunction, and maladaptive neuroimmune-autonomic signaling.

### 4. Knowledge gaps and future directions

Despite increasing recognition of GRDs as systemic conditions, major knowledge gaps remain regarding their



**Figure 5.** Systemic clinical manifestations and differential responses to dietary intervention. This flowchart contrasts the multisystem impact of active gluten-related disorders with outcomes following therapeutic dietary treatment. (A) Active gluten-related disorders maintain barrier disruption and systemic inflammation, yielding malabsorption and extra-intestinal neurological (e.g., ataxia, cognitive impairment) and cardiovascular (e.g., arrhythmias, ischemic events) complications. (B) A gluten-free diet fosters mucosal healing, barrier restoration, and reduced immune signaling, often improving neurocardiac symptoms, although some patients experience persistent signs, suggesting structural damage, central sensitization, or refractory inflammation requiring adjunctive strategies. Image created using GPAI Pro and BioRender.com.

impact on the brain–heart axis. Mechanistic studies directly linking gluten exposure to defined neurocardiac outcomes remain limited, with most available data derived from observational or associative research, thereby restricting causal inference. In particular, the biological pathways connecting intestinal immune activation with autonomic regulation, vascular function, and cardiac electrophysiology remain incompletely characterized. Available evidence is unevenly distributed across the GRD spectrum. Celiac disease is relatively well studied, whereas NCGS and wheat allergy remain markedly underrepresented in neurological and cardiovascular research. This imbalance limits generalizability and hampers the development of phenotype-specific risk stratification strategies.

In addition, autonomic and neurovascular dysfunction are inconsistently assessed across studies, reflecting the lack of standardized diagnostic tools and outcome measures applicable to clinical and research settings. Furthermore, dedicated burden-of-disease analyses quantifying disability-adjusted life years attributable to the full GRD spectrum—considering symptom severity, treatment adherence, and regional disparities in diagnosis

and healthcare access—are a critical priority to establish the true population-level impact of these conditions and inform public health resource allocation.<sup>58</sup>

A critical unmet need is the development and validation of non-invasive biomarkers capable of detecting subclinical neurocardiac involvement and monitoring treatment response. Candidate markers may include circulating neurofilament light chain for neuronal injury<sup>59</sup>, high-sensitivity cardiac troponin for myocardial stress, and advanced autonomic function indices<sup>60</sup>, although their clinical utility in GRDs requires prospective validation.

Importantly, brain–heart outcomes are rarely incorporated as predefined endpoints in clinical trials evaluating dietary or adjunctive interventions in GRDs. As a result, the reversibility, persistence, and clinical significance of neurocardiac alterations remain poorly defined. Future research should therefore adopt multimodal, systems-level approaches integrating immunological profiling, autonomic testing, neuroimaging, and cardiovascular assessment. In particular, larger, multi-ethnic, sex-stratified cohort studies are needed to define whether racial and ethnic differences in disease presentation, immune

phenotype, and age-related clinical trajectories translate into divergent susceptibility to neurocardiac manifestations in GRDs. Such designs are essential to delineate shared mechanisms, identify clinically meaningful biomarkers, and inform targeted, personalized management strategies for patients with GRDs.

## 5. Limitations

This narrative review has several limitations that should be considered when interpreting its conclusions. First, by design, narrative reviews do not employ the exhaustive, protocol-driven search strategies or formal risk-of-bias assessments characteristic of systematic reviews. Although this review was conducted and reported in accordance with SANRA principles, the possibility of incomplete literature capture cannot be entirely excluded. To mitigate this limitation, the review objectives were clearly defined a priori, the narrative format was explicitly justified, and evidence selection emphasized conceptual relevance, methodological robustness, and balanced interpretation in line with SANRA criteria.

Second, the heterogeneity of GRDs—including autoimmune, innate immune-mediated, and IgE-mediated phenotypes—limits the ability to draw uniform mechanistic conclusions, particularly with respect to brain–heart interactions. Available evidence is unevenly distributed across disease entities, with celiac disease substantially overrepresented compared with NCGS and wheat allergy. As a result, conclusions pertaining to non-celiac entities should be interpreted with appropriate caution.

Moreover, much of the literature addressing neurological, autonomic, and cardiovascular involvement in GRDs is observational or hypothesis-generating in nature. This limits causal inference and increases susceptibility to residual confounding, particularly in studies evaluating complex outcomes such as autonomic function or cardiovascular risk. Additionally, publication bias may favor positive associations, particularly for rare or novel extra-intestinal manifestations, potentially leading to overestimation of effect sizes and clinical significance.

Finally, the integration of brain and heart outcomes is constrained by variability in outcome definitions, non-standardized assessment tools, and inconsistent reporting across studies. These factors restrict cross-study comparability and synthesis. Despite these limitations, adherence to SANRA standards supports the methodological credibility of this review and underscores its role in providing a coherent conceptual framework, identifying knowledge gaps, and informing the design of future mechanistic and translational research rather than delivering definitive effect estimates.

## 6. Conclusion

Gluten-related disorders manifest systemic immune-mediated effects that extend beyond the gastrointestinal tract to include the central nervous system and cardiovascular system. Evidence implicates interconnected mechanisms involving immune activation, barrier dysfunction, and autonomic dysregulation in driving neurological, psychiatric, and cardiovascular manifestations. Conceptualizing GRDs through a gut–brain–heart axis unifies these immunological and neurovascular processes and clarifies that extra-intestinal features are integral to disease expression. Clinically, prompt recognition of systemic involvement and strict adherence to a GFD are crucial, with early intervention enabling partial reversibility of selected neurocardiac alterations. However, persistence of symptoms in a substantial minority underscores the need for comprehensive evaluations and adjunctive therapies. Interdisciplinary research integrating immunology, neuroscience, and cardiology is essential to refine pathophysiological understanding, improve risk stratification, and facilitate personalized care for individuals with GRDs.

## List of abbreviations

| Abbreviation | Definition                                            |
|--------------|-------------------------------------------------------|
| BBB          | Blood–brain barrier                                   |
| CD4          | Cluster of differentiation 4                          |
| GFD          | Gluten-free diet                                      |
| GRD          | Gluten-related disorder                               |
| HLA          | Human leukocyte antigen                               |
| Ig           | Immunoglobulin                                        |
| SANRA        | Scale for the Assessment of Narrative Review Articles |
| TG2          | Tissue transglutaminase 2                             |

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