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Adverse Food Reactions from Mechanisms to Management: A PRISMA Systematic Review of IgE-Mediated Allergies, Autoimmune Enteropathies, and Non-Immune Intolerances

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ABSTRACT: Background: Adverse reactions to food represent one of the most prevalent and clinically consequential issues in modern medicine. They encompass two fundamentally distinct categories: food allergy, an immune-mediated hypersensitivity, and food intolerance, driven by non-immune enzymatic, pharmacological, or metabolic mechanisms. As the global burden of both conditions continues to rise, driven primarily by environmental and lifestyle factors, a comprehensive and evidence-based synthesis of the literature is urgently needed.

Objectives: This systematic review aims to identify and synthesize the full spectrum of foods known to cause allergy or intolerance, characterize their underlying immunological

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and biochemical mechanisms, summarize current diagnostic criteria, and appraise the evidence base for management strategies.

Methods: A comprehensive search of PubMed/MEDLINE, Embase, Scopus, and Cochrane Library was conducted. Studies from January 2015 to May 2026 were prioritized, with seminal earlier publications included where essential. Search terms included: food allergy, food hypersensitivity, food intolerance, IgE-mediated, celiac disease, lactose intolerance, FODMAP, anaphylaxis, allergen, combined with specific food categories. PRISMA 2020 guidelines were followed throughout.

Results: Food allergy affects approximately 8% of children and 10% of adults globally, with the prevalence rising in developed nations. Nine major food allergens account for over 90% of reactions: peanut, tree nuts, milk, egg, wheat, soy, fish, shellfish, and sesame. Food intolerances, including lactose intolerance (affecting ~68% of the world population), non-celiac gluten sensitivity, fructose malabsorption, FODMAP sensitivity, and histamine intolerance, are distinct from true allergy in their non-immune mechanisms. Celiac disease, a gluten-triggered autoimmune enteropathy, occupies a unique intermediate category. Current diagnostic gold standards include oral food challenge (OFC) for allergy and hydrogen breath testing for carbohydrate intolerances.

Conclusions: A clear mechanistic distinction between food allergy and intolerance is essential for accurate diagnosis and effective management. Patient morbidity—physical, psychological, and nutritional—is substantial. Unvalidated commercial tests contribute to unnecessary dietary restriction. Evidence-based diagnosis and multidisciplinary management remain the cornerstone of care.

1. INTRODUCTION

Adverse food reactions have become one of the most pressing concerns in global public health. Historically perceived as rare nuisances, food allergies and intolerances now affect hundreds of millions of individuals worldwide, profoundly affecting quality of life, nutrition, mental health, and healthcare systems. [1] The distinction between the two—food **allergy** (immune-mediated) and food **intolerance** (non-immune)—is not merely semantic. It has direct and consequential implications for how patients are investigated, counselled, treated, and monitored.

Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly upon exposure to a given food. [2] The dominant mechanism is immunoglobulin E (IgE)-mediated sensitization and mast cell degranulation, though non-IgE-mediated and mixed mechanisms also contribute substantially. [3] In stark contrast, food intolerance arises from pharmacological, enzymatic, or metabolic defects and does not involve the adaptive immune system. [4] Despite their mechanistic differences, these conditions are clinically intertwined, frequently misdiagnosed, and too often managed through empirical self-imposed dietary restrictions unsupported by validated diagnostic testing. [5]

The global rise in food allergy prevalence over the past three decades—particularly striking in Westernized nations—is thought to reflect the intersection of genetic susceptibility with rapidly shifting environmental exposures including the hygiene hypothesis, early dietary patterns, microbiome disruption, and modern food processing. [1][6] Meanwhile, food intolerances such as lactose malabsorption, histamine intolerance, and non-celiac gluten sensitivity remain incompletely understood, diagnostically uncertain, and often managed through restrictive diets that carry their own nutritional risks.[7]

This systematic review seeks to provide the most complete and evidence-based synthesis of the current literature on all foods associated with allergy or intolerance, organizing them by mechanism, prevalence, clinical presentation, and management.

2. METHODS

2.1 Search Strategy

A systematic search was conducted in accordance with PRISMA 2020 guidelines across PubMed/MEDLINE, Embase, Scopus, and Cochrane Library, supplemented by hand-searching of reference lists from key reviews. [8] Search terms combined MeSH headings and free-text terms: "food allergy," "food hypersensitivity," "food intolerance," "IgE-mediated," "anaphylaxis," "celiac disease," "lactose intolerance," "FODMAP," "gluten sensitivity," "allergen," "histamine intolerance," along with the names of individual food categories (peanut, milk, egg, wheat, shellfish, fish, sesame, soy, tree nut, lupin, celery, mustard, mollusc, sulphite). Publication date limits: January 2015 to May 2026, with seminal earlier publications included where foundational.

2.2 Inclusion and Exclusion Criteria

Studies were included if they: (a) examined IgE- or non-IgE-mediated food allergy, celiac disease, or food intolerance; (b) reported prevalence, mechanisms, diagnostic approaches, or treatment outcomes; (c) were conducted in human populations; (d) were systematic reviews, meta-analyses, randomized controlled trials, cohort studies, case-control studies, or authoritative clinical guidelines.

Exclusion criteria included: animal-only studies without human translational data, case reports of rare idiosyncratic reactions not meeting allergy or intolerance criteria, review articles lacking primary data, and studies published exclusively in languages unavailable for translation.

2.3 Data Extraction and Quality Assessment

Two independent reviewers extracted data on food type, population characteristics, prevalence estimates, immunological or biochemical mechanisms, diagnostic criteria, and therapeutic interventions. Quality was assessed using the Newcastle-Ottawa Scale for observational studies and the AMSTAR-2 checklist for systematic reviews. Disagreements were resolved by consensus or a third reviewer.

3. FOOD ALLERGY: MECHANISMS, CLASSIFICATION, AND EPIDEMIOLOGY

3.1 Immunological Framework

Food allergy is a disorder of immune dysregulation in which the body mounts an inappropriate and specific immune response against ordinarily harmless dietary proteins. [2] The classification into IgE-mediated, non-IgE-mediated, and mixed mechanisms has profound practical implications.

IgE-mediated reactions represent the classic and most acute form of food allergy. Upon first exposure to a food allergen, sensitized individuals produce allergen-specific IgE antibodies that bind to high-affinity FcεRI receptors on mast cells and basophils. [3] On re-exposure, crosslinking of surface-bound IgE by the allergen triggers rapid degranulation, releasing histamine, tryptase, prostaglandins, leukotrienes, and cytokines. [9] Clinical manifestations typically appear within minutes and may range from localized urticaria to life-threatening systemic anaphylaxis. [32] Investigations of near-fatal and fatal food-induced anaphylaxis indicate that peanuts, tree nuts, and shellfish account for the majority of severe reactions, though milk has been increasingly reported as a cause, particularly in children. [32]

Non-IgE-mediated reactions are predominantly T-cell mediated and present with delayed symptoms (hours to days) predominantly in the gastrointestinal tract. Key conditions include food protein–induced enterocolitis syndrome (FPIES), food protein–induced allergic proctocolitis, and eosinophilic gastrointestinal disorders. [3] These conditions are frequently underdiagnosed due to the absence of specific biomarkers.

Mixed IgE/non-IgE mechanisms are characteristic of conditions such as eosinophilic esophagitis (EoE), in which both immediate IgE-mediated and delayed T-cell-mediated pathways contribute to inflammation and tissue remodeling. [2]

It is the protein component—not the fat or carbohydrate—of foods that drives sensitization. Allergenic proteins tend to be small (10–70 kDa), water-soluble glycoproteins resistant to denaturation by heat, acid, and digestion, enabling them to remain intact through processing, cooking, and the gastrointestinal tract. [34]

3.2 Global Prevalence and Trends

Food allergy is a major public health issue globally, affecting approximately 8% of children and 10% of adults in developed countries. [1] The prevalence varies markedly between geographic regions, reflecting differences in genetic backgrounds, dietary exposures, environmental factors, and diagnostic methodology. [4] The increase in prevalence is driven mainly by environmental factors, possibly together with genetic susceptibility to environmental changes. [6] A 2023 systematic review and meta-analysis of European data found significant variation in allergen-specific prevalence across the 14 most regulated allergens. [4]

In children, approximately 90% of food allergies are attributed to cow's milk, egg, soy, wheat, peanut, tree nuts, fish, and shellfish. In adults, shellfish, fish, peanuts, and tree nuts are most commonly implicated. [32] The natural history differs by allergen: cow's milk, egg, and wheat allergies in young children carry a more favorable prognosis with relatively early resolution, while peanut, tree nut, and seafood allergies are more likely to be persistent and lifelong. [37]

Cross-reactive epitopes further complicate the epidemiology. Shellfish, fish, tree nuts, and peanuts show very high cross-reactivity rates; peanut allergy increases the risk of tree nut allergy to 20–50%, and cross-reactivity with sesame and lupin is also documented. [39][16] The allergen-specific lifelong persistence of IgE resides in the persistence of allergen-specific memory B cells, which serve as the chief reservoir for IgE regeneration. [38]

Table 1. Major food allergen regulatory frameworks by jurisdiction.

Jurisdiction	Number of Priority Allergens	Legislative Framework
USA	9 (as of 2023)	FALCPA 2004; FASTER Act 2021
European Union	14	EU Regulation No. 1169/2011
Canada	11	Food and Drug Regulations
Australia / New Zealand	14	Australia New Zealand Food Standards Code

3.3 Major Food Allergens: A Systematic Description

3.3.1 Peanut (Arachis hypogaea)

Peanut allergy (PA) is among the most common and feared food allergies in developed countries, representing a leading cause of food-induced anaphylaxis and allergy-related deaths among children. [36] Unlike the childhood allergies to milk and egg, peanut allergy resolves in only approximately 20% of individuals, rendering it largely lifelong. [1] The major peanut allergens—Ara h 1, 2, 3, 6—are seed storage proteins of high clinical relevance. Ara h 2 is the most diagnostically sensitive component: allergen component testing using Ara h 2-specific IgE has shown high specificity in Western Europe. [35] The gut microbiome's capacity to metabolize peanut proteins (e.g., by oral Rothia species) may modulate the severity of anaphylactic reactions, a promising emerging research direction. [36]

3.3.2 Tree Nuts

Tree nut allergy encompasses reactions to almonds, hazelnuts, walnuts, cashews, pecans, Brazil nuts, pistachios, and macadamia nuts—all regulated under EU Annex II. [21] Key allergens include Cor a 14 (hazelnut) and Ana o 3 (cashew), both of which are diagnostically informative components. [35] Cross-reactivity among tree nuts is high; however, having a peanut allergy increases—not guarantees—the risk of tree nut allergy. [39] Tree nut allergy is typically lifelong and accounts for a disproportionate fraction of severe anaphylaxis admissions in adults. [32]

3.3.3 Cow's Milk

Cow's milk allergy (CMA) is the most common food allergy in infancy, estimated to affect 2–3% of children under age 3. [20] Both IgE-mediated (immediate) and non-IgE-mediated (delayed) reactions occur. The main allergenic proteins are caseins and whey proteins, particularly β-lactoglobulin and α-lactalbumin. [34] CMA has a generally favorable prognosis, with approximately

80% of affected children achieving tolerance by school age. [37] However, milk has been increasingly reported as a cause of fatal or near-fatal anaphylaxis, particularly in children with severe asthma as a comorbidity. [32] Management involves milk protein elimination and periodic reassessment using baked milk challenges, since tolerance to baked milk proteins often precedes tolerance to raw milk.[37]

3.3.4 Hen's Egg

Egg allergy affects approximately 9% of infants at age one year—the peak of sensitization—declining markedly to approximately 1.2% by age six in longitudinal population studies such as the Australian HealthNuts study. [1] The major egg white allergens include ovalbumin and ovomucoid (Gal d 1); ovomucoid's heat stability is clinically significant, as its persistence upon cooking correlates with sensitivity to baked egg. [34] Egg allergy is strongly associated with atopic dermatitis and may complicate influenza vaccination in sensitized children, though this risk is now considered minimal at standard thresholds. [37]

3.3.5 Wheat and Gluten-Related Disorders

Wheat allergy (WA) is an IgE- or non-IgE-mediated hypersensitivity to wheat proteins (omega-5 gliadin, gliadins, glutenins) that is distinct from celiac disease and non-celiac gluten sensitivity. [28] Wheat-dependent, exercise-induced anaphylaxis (WDEIA) is a notable phenotype, predominantly mediated by omega-5 gliadin sensitization. [28] Wheat allergy in children is more commonly outgrown than peanut or tree nut allergy. [37]

It must be emphasized that **wheat allergy, celiac disease, and non-celiac gluten sensitivity are three distinct conditions** sharing the same dietary trigger (gluten-containing grains) but differing fundamentally in their immune mechanisms, natural history, and clinical management. [28] Wheat allergy involves classic IgE or cell-mediated immune responses; celiac disease is an HLA-restricted autoimmune enteropathy; and NCGS is a diagnosis of exclusion involving innate immune activation. [24][28]

3.3.6 Soy

Soy allergy is common in infancy and childhood, often co-occurring with cow's milk allergy due to cross-reactive proteins. [34] The major soy allergens are Gly m 5 and Gly m 6, seed storage proteins. Anaphylaxis is rare but possible. [32] Most children outgrow soy allergy, and strict elimination is often not required for mild reactions. [37]

3.3.7 Fish

Fish allergy is predominantly mediated by parvalbumin, a highly conserved and heat-stable calcium-binding protein (prototype: Gad c 1 from cod). [34] Cross-reactivity across fish species is common, though some individuals tolerate certain species selectively. [39] Fish allergy typically persists into adulthood and can manifest through ingestion, skin contact, or inhalation of cooking vapors, the latter being particularly relevant in occupational settings.[32]

3.3.8 Shellfish

Shellfish allergy encompasses both crustaceans (shrimp, crab, lobster, prawn) and molluscs (mussels, oysters, squid, abalone). [15] The primary allergen is tropomyosin, a muscle protein highly conserved across invertebrates, which explains cross-reactivity between crustaceans and molluscs. [34] Shellfish allergy is the most prevalent food allergy in adults globally and is associated with particularly high rates of severe anaphylaxis. Reactions can be triggered not only by ingestion but also by aerosolization of cooking proteins. [20]

3.3.9 Sesame

Sesame (*Sesamum indicum*) allergy has gained increased regulatory attention, recognized as the 9th major food allergen in the United States under the FASTER Act of 2021, effective January 2023. [19] The key allergens are Ses i 1, 2, and 3. Sesame allergy often persists into adulthood and is associated with reactions in individuals already sensitized to peanut and lupin due to shared lipid transfer protein (LTP) epitopes. [16][39]

3.3.10 Additional EU-Regulated Allergens

European Union Regulation No. 1169/2011 mandates declaration of 14 allergens, including several not formally recognized in the US framework. [21]

- **Celery (Apium graveolens):** Sensitization often occurs via cross-reactivity with birch pollen (Bet v 1 homologue); reactions range from oral allergy syndrome to systemic anaphylaxis. Particularly prevalent in Central Europe.
- **Mustard:** A potent allergen in both condiment and seed form; cross-reactive with peanut and lupin. Sensitization via LTP is the dominant pathway in Mediterranean populations.
- **Lupin (Lupinus spp.):** Increasingly used as a gluten-free flour substitute, lupin poses a cross-reactive risk for peanut-allergic individuals. Used in biscuits, pasta, and meat products. [16]
- **Molluscs:** Allergenically distinct from crustaceans but sharing tropomyosin; cross-reactivity with crustaceans is variable. Regulated separately under EU law.
- **Sulphur dioxide and sulphites (>10 mg/kg):** Used as preservatives in wine, dried fruit, and processed foods. Can trigger bronchospasm in asthmatic individuals via neurogenic or oxidative mechanisms, constituting a pharmacological rather than immunological intolerance. [21]

Table 2. Summary characteristics of major food allergens.

Allergen	Key Proteins	Mechanism	Common Symptoms	Persistence
Peanut	Ara h 1, 2, 3, 6	IgE-mediated	Urticaria, angioedema, anaphylaxis	Lifelong ~80%
Tree nuts	Cor a 14, Ana o 3	IgE-mediated	Anaphylaxis, oral allergy syndrome	Lifelong
Cow's milk	Casein, β-lactoglobulin	IgE&non-IgE	GI, skin, respiratory	Resolved by age 5 in ~80%
Hen's egg	Ovalbumin, ovomucoid	IgE-mediated	Urticaria, eczema, anaphylaxis	Often outgrown by age 6
Wheat	Gliadins, glutenins	IgE&non-IgE; autoimmune (CD)	Urticaria, GI, asthma (WDA)	Often outgrown
Soy	Gly m 5, 6	IgE-mediated	Mild; anaphylaxis rare	Often outgrown
Fish	Parvalbumin (Gad c 1)	IgE-mediated	Urticaria, anaphylaxis, FPIES	Lifelong
Shellfish	Tropomyosin	IgE-mediated	Anaphylaxis, skin, respiratory	Lifelong
Sesame	Ses i 1, 2, 3	IgE-mediated	Urticaria, angioedema, anaphylaxis	Often lifelong

4. FOOD INTOLERANCE: MECHANISMS, SPECTRUM, AND MANAGEMENT

Food intolerance affects an estimated 15–20% of the general population and arises through three principal non-immune mechanisms: (1) enzyme or transport defects; (2) pharmacological effects of food chemicals; and (3) poorly defined metabolic pathways. [8] Unlike food allergy, intolerances are typically dose-dependent, do not involve IgE, and are rarely life-threatening. Nevertheless, they cause substantial morbidity, impair quality of life, and frequently lead patients to unnecessary and nutritionally harmful self-restriction. [10]

4.1 Lactose Intolerance

Lactose intolerance is the most prevalent food intolerance globally, estimated to affect approximately 65–68% of the world's adult population, with extreme variation by ethnicity: prevalence reaches 95–100% in some East Asian and West African populations, 50% in South America and Southern Europe, and as low as 2% in Scandinavia. [42][48] This variation is rooted in the LCT gene and the MCM6 regulatory region, which in 'lactase persistence' phenotypes maintain intestinal lactase–phlorizin hydrolase (LPH) activity into adulthood due to the derived alleles C/T-13910 and G/A-22018. [13]

In lactose malabsorption, unhydrolyzed lactose passes to the colon, where it generates osmotic load and undergoes bacterial fermentation, producing short-chain fatty acids and gases (hydrogen, methane, carbon dioxide). [48] The characteristic symptoms are abdominal pain (reported in approximately 71% of affected individuals), bloating (66%), diarrhea (30%), and flatulence (29%). [46] Symptom severity is subjective and depends on the residual lactase concentration, intestinal motility, amount of lactose ingested, and individual visceral sensitivity. [48] The hydrogen breath test (HBT) is the routinely used diagnostic standard; genetic testing for the C/T-13910 polymorphism provides complementary evidence. [13] Lactose-intolerant individuals should not necessarily eliminate all dairy; low-lactose products, hard cheeses, and fermented dairy such as yoghurt are typically well tolerated.[44]

4.2 Fructose Malabsorption

Fructose malabsorption results from deficient activity of the GLUT5 intestinal fructose transporter, leading to incomplete absorption of dietary fructose. [9] Unabsorbed fructose causes colonic osmotic load and fermentation, producing symptoms indistinguishable from lactose intolerance. Prevalence in the Western population is estimated at 30–40% by breath testing, though symptom-causing fructose intolerance is lower. [8] Hereditary fructose intolerance (HFI), a distinct and rare autosomal recessive deficiency of aldolase B, presents in infancy with severe hypoglycemia and hepatotoxicity upon fructose exposure. [10] HFI carries a validated diagnostic test (fructose tolerance test) and requires strict fructose elimination.[10]

4.3 FODMAP Sensitivity

Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols (FODMAPs) are a diverse group of short-chain carbohydrates poorly absorbed in the small intestine. They include: fructans and galacto-oligosaccharides (GOS) from wheat, onions, garlic, and legumes; lactose from dairy; fructose in excess of glucose from apples and honey; and polyols (sorbitol, mannitol, xylitol) from stone fruit and sugar-free products. [12]

FODMAP sensitivity has strong mechanistic evidence: poorly absorbed FODMAPs increase luminal osmotic activity (drawing water into the gut) and are rapidly fermented by colonic bacteria, producing gas and intestinal distension. [9] In individuals with visceral hypersensitivity—as in irritable bowel syndrome (IBS)—this leads to pain, bloating, altered bowel habits, and flatulence. [11] The low-FODMAP diet, implemented under dietitian supervision as a three-phase protocol (restriction, reintroduction, personalization), is the most evidence-based dietary intervention for IBS-related symptoms, demonstrating efficacy in 50–80% of patients. [8] However, a low-FODMAP diet affects the gastrointestinal microbiota and must not be sustained indefinitely without dietary reintroduction. [8]

Importantly, restricting fructans (a component from the carbohydrate fraction of wheat) in the context of a low-FODMAP diet is suggested as a first step in patients with non-celiac wheat sensitivity, while further clinical trials are needed to clarify the full dietary approach required. [7]

4.4 Non-Celiac Gluten/Wheat Sensitivity (NCGS/NCWS)

NCGS is a clinical syndrome in which gluten-containing foods trigger gastrointestinal and extraintestinal symptoms (fatigue, 'brain fog,' headache, joint pain, skin changes) in the absence of celiac disease or wheat allergy. [28] It is a diagnosis of exclusion: celiac disease must be ruled out serologically and, if appropriate, histologically, and wheat allergy must be excluded by IgE testing. [10] Unlike celiac disease, NCGS does not cause villous atrophy; instead, innate immune activation and increased intestinal permeability appear to play pathogenic roles. [28]

The overlap between IBS and gluten-related disorders, together with placebo and nocebo responses, makes accurate diagnosis profoundly challenging. A randomized crossover trial demonstrating symptom recurrence with gluten re-challenge compared

with placebo is the methodological gold standard, but is rarely achievable in clinical practice. [7] Current estimates suggest NCGS affects 0.5–13% of the population, though precise figures are difficult to ascertain given the lack of a validated biomarker. [10]

4.5 Celiac Disease (Autoimmune Gluten Enteropathy)

Celiac disease (CD) occupies a unique position at the interface of allergy and intolerance: it is neither a classical allergy (no IgE involvement) nor a simple intolerance, but rather a T-cell-mediated autoimmune enteropathy. It is classified here among intolerances because the trigger is a dietary antigen (gluten) rather than a classic immunogen. [30]

CD has a global prevalence estimated at 0.75–1.6% of the general population, with diagnosis rising as serological screening becomes more widespread. [30] Genetic susceptibility is obligatory: over 95% of patients carry HLA-DQ2 (encoded by DQA1*05:01/DQB1*02:01) or HLA-DQ8 (DQA1*03:01/DQB1*03:02) haplotypes, though these are necessary but not sufficient for disease development. [24]

The immunopathological cascade begins when gliadin peptides cross the intestinal epithelial barrier and are deamidated by tissue transglutaminase 2 (tTG2), converting neutral glutamine residues to negatively charged glutamate. [27] This modification increases peptide affinity for HLA-DQ2/DQ8 molecules on antigen-presenting cells, enabling presentation to gliadin-reactive CD4+ T cells. [27] Interleukin-15 plays a central regulatory role, stimulating intraepithelial lymphocyte activation and acquisition of NK-cell markers, ultimately driving epithelial apoptosis and villous atrophy. [25] The result is villous atrophy, crypt hyperplasia, and malabsorption—the histological hallmark of CD. [24]

CD presents as a systemic disease with gastrointestinal manifestations (diarrhea, steatorrhea, weight loss, bloating), non-gastrointestinal manifestations (dermatitis herpetiformis, gluten ataxia, peripheral neuropathy, osteoporosis, infertility, iron-deficiency anemia), and a silent form where histological damage exists in the absence of overt symptoms. [29] Diagnosis relies on anti-tissue transglutaminase IgA (tTG-IgA) antibody testing (sensitivity ~95%, specificity ~95%) as the screening tool, with upper endoscopy and duodenal biopsy (Marsh classification) as the gold standard. [29] The only established treatment is a lifelong, strict gluten-free diet; low adherence rates necessitate ongoing research into pharmacological adjuncts. [24]

4.6 Histamine Intolerance

Histamine intolerance results from an imbalance between dietary histamine load and the body's capacity to degrade it, primarily through the enzyme diamine oxidase (DAO) and, to a lesser extent, histamine N-methyltransferase (HNMT). [7] Foods with the highest histamine content include aged and fermented products: red wine, aged cheeses, fermented meats, sauerkraut, vinegar, and canned fish. [7] Symptom manifestations are protean and include headache, urticaria, flushing, nasal congestion, diarrhea, and dysmenorrhea. [9] Diagnosis is challenging; DAO serum assay (cutoff typically 3 U/mL) provides supporting evidence, but a structured elimination diet followed by blinded rechallenge is the most clinically useful approach. [10]

4.7 Sulphite Sensitivity

Sulphites (sulphur dioxide, sodium and potassium bisulphite and metabisulphite) are widely used as antimicrobial and antioxidant preservatives in wine, dried fruit, molasses, and many processed foods. [21] Reactions in sensitized individuals—particularly those with underlying asthma—include bronchospasm, urticaria, and, rarely, anaphylaxis. [17] The mechanism is incompletely understood but likely involves neurogenic bronchoconstriction, stimulation of sensory airways, or toxic effects on sulphite oxidase–deficient individuals. [9] EU and US regulations mandate declaration when sulphite content exceeds 10 mg/kg; this threshold forms the basis of current risk management. [21]

4.8 Other Foods and Emerging Intolerances

4.8.1 Caffeine Sensitivity

Caffeine metabolism depends heavily on the CYP1A2 enzyme and adenosine receptor genetics. Slow metabolizers experience amplified central nervous system stimulation, cardiovascular palpitations, insomnia, and anxiety at doses tolerated by rapid metabolizers. While not immune-mediated, caffeine sensitivity causes significant morbidity in susceptible individuals and is relevant to coffee, tea, energy drinks, and chocolate consumption.[10]

4.8.2 Food Additive Intolerances

A range of artificial colorants (tartrazine, sunset yellow), preservatives (benzoates, nitrites), flavor enhancers (monosodium glutamate—though the 'Chinese restaurant syndrome' evidence is contested), and sweeteners (aspartame) have been implicated in intolerance reactions. [9] Reproducible, double-blind placebo-controlled evidence for many of these associations remains sparse, and unvalidated claims propagate unnecessary restriction. [11]

4.8.3 Emerging Allergens: Alpha-gal Syndrome

Alpha-gal syndrome (AGS) represents one of the most clinically novel and mechanistically unique forms of food allergy discovered in the 21st century. [2] Sensitization to the carbohydrate epitope galactose-alpha-1,3-galactose (alpha-gal) occurs following tick bites (predominantly Amblyomma americanum in the US and Ixodes ricinus in Europe), triggering delayed IgE-mediated reactions—typically 3–6 hours after consumption—to red meat (beef, pork, lamb), organ meats, and some mammalian-derived products such as dairy in highly sensitized individuals.[2]

Table 3. Characteristics of major food intolerances.

Intolerance	Implicated Food	Mechanism	Symptoms	Diagnosis
Lactose intolerance	Dairy products	Lactase enzyme deficiency	Bloating, diarrhea, cramping	Hydrogen breath test; lactase gene assay
Fructose intolerance	Fruit, honey, HFCS	GLUT5 transporter defect	Bloating, flatulence, diarrhea	Fructose breath test
FODMAP sensitivity	Wheat, onion, legumes, some fruits	Osmotic load + fermentation	IBS-type symptoms, visceral pain	Dietary exclusion (Rome IV)
Histamine intolerance	Fermented/aged foods, red wine, fish	Low diamine oxidase (DAO) activity	Headache, flushing, urticaria, GI	DAO assay; elimination diet
NCGS / wheat sensitivity	Wheat, barley, rye	Innate immune activation; non-IgE	Fatigue, brain fog, GI symptoms	Exclusion of CD&WA; elimination
Celiac disease	Wheat, rye, barley (gluten)	T-cell autoimmune; HLA-DQ2/DQ8	Villous atrophy, malabsorption, diarrhea	tTG-IgA antibody; duodenal biopsy
Sulphite sensitivity	Wine, dried fruit, processed food	SO_2 inhibits enzymes; neurogenic	Asthma, urticaria, headache	Provocation test; clinical history
Caffeine sensitivity	Coffee, tea, energy drinks, chocolate	CYP1A2 gene variation; adenosine antagonism	Palpitations, anxiety, insomnia	Clinical history; elimination

5. DIAGNOSIS OF FOOD ALLERGY AND INTOLERANCE

Accurate diagnosis is foundational. Misdiagnosis—which in clinical practice is common—leads to either failure to treat genuine allergy (risking anaphylaxis) or unnecessary elimination diets that compromise nutrition, social function, and quality of life. [5]

The EAACI 2023 guidelines on the diagnosis of IgE-mediated food allergy recommend a stepwise approach: clinical history, then IgE sensitization testing (SPT and/or serum sIgE), and oral food challenge when uncertainty persists. [35]

5.1 Allergy Diagnosis

An allergy-focused clinical history remains the critical first step, assessing the temporal relationship between food consumption and symptom onset, reproducibility, severity, and potential confounders such as exercise or alcohol. [35]

Skin prick test (SPT): A wheal ≥3 mm greater than the saline control confirms sensitization but not necessarily clinical allergy. Sensitivity is generally high but specificity is lower. [35]

Serum allergen-specific IgE (sIgE): Immunoassay-based quantification of food-specific IgE. Component-resolved diagnostics (CRD)—measuring IgE to specific molecular allergens such as Ara h 2 for peanut, Cor a 14 for hazelnut, and Ana o 3 for cashew—provide superior diagnostic accuracy compared to whole-extract testing, especially in pollen-sensitized individuals. [35]

Basophil activation test (BAT): A functional assay measuring CD63 or CD203c upregulation on basophils upon allergen stimulation. The BAT has shown high specificity for peanut and milk allergy and serves as a valuable adjunct when SPT/sIgE results are equivocal. [1]

Oral food challenge (OFC): The gold standard for food allergy diagnosis, providing approximately 97% diagnostic accuracy. OFC is performed under supervised medical conditions with graded, incremental allergen administration. It is recommended when the history and test results are discordant, when allergy resolution is being assessed, or when allergen restriction is to be initiated or lifted. [1][35]

5.2 Celiac Disease Diagnosis

Serological screening with anti-tTG IgA antibody (on a gluten-containing diet) is the first-line test, with total serum IgA measured simultaneously to exclude IgA deficiency. Anti-deamidated gliadin peptide (DGP) IgG is the preferred test in IgA-deficient patients. [24] Duodenal biopsy with histological grading (Marsh score 0–3) remains the gold standard for definitive diagnosis. HLA-DQ2/DQ8 typing is used to exclude CD in equivocal cases (a negative result has a high negative predictive value). [29]

5.3 Intolerance Diagnosis

For carbohydrate intolerances (lactose, fructose), the hydrogen and/or methane breath test is the validated and widely available diagnostic standard, measuring exhaled gas after an oral carbohydrate load. [8] For NCGS and FODMAP sensitivity, no biomarker exists; diagnosis requires structured exclusion of celiac disease and wheat allergy, followed by a supervised dietary elimination and blinded rechallenge. [10] For histamine intolerance, DAO activity measurement in serum (<3 U/mL is the most commonly used threshold) combined with a structured elimination diet provides the highest diagnostic yield. [7]

A critical point that the literature emphasizes is that many commercial 'food intolerance tests' (IgG panel testing, hair analysis, applied kinesiology, and bioresonance) lack any validated evidence base and are strongly discouraged by scientific consensus. [10] Their results lead to unwarranted and potentially harmful dietary restrictions, increasing the risk of nutritional deficiencies and negatively affecting quality of life. [5]

Table 4. Diagnostic tools for food allergy and intolerance.

Test	Condition	Sensitivity / Specificity	Gold Standard?
Skin prick test (SPT)	IgE-mediated food allergy	High sensitivity; variable specificity	No; confirms sensitisation
Serum specific IgE (sIgE)	IgE-mediated food allergy	Allergen-dependent (e.g. peanut ~95% PPV)	No; requires OFC confirmation

Test	Condition	Sensitivity / Specificity	Gold Standard?
Basophil activation test (BAT)	IgE-mediated (adjunct)	High specificity for peanut, milk	No; adjunctive role
Oral food challenge (OFC)	All food allergies	Gold standard; ~97% accuracy	Yes
tTG-IgA serology	Celiac disease	Sensitivity ~95%, Specificity ~95%	No; duodenal biopsy is gold standard
Hydrogen breath test (HBT)	Lactose / fructose intolerance	Sensitivity 68–78%; specificity 83–100%	Yes (for lactose)
Elimination + rechallenge diet	NCGS, FODMAP, histamine intolerance	Best available for non-immune intolerances	Yes (for many intolerances)

6. MANAGEMENT

6.1 Allergen Avoidance and Emergency Preparedness

For all confirmed food allergies, strict elimination of the offending allergen remains the only universally applicable management strategy. [34] Patients with a history of systemic reactions must carry self-injectable epinephrine (adrenaline) and be trained in its use; epinephrine administered by intramuscular injection into the lateral thigh is the treatment of choice for anaphylaxis. [34] Antihistamines and corticosteroids have no role as first-line emergency treatment for anaphylaxis, though they may reduce delayed symptoms. Patients, caregivers, and—crucially—school personnel should receive structured training in allergy management.[6]

6.2 Allergen Immunotherapy

Oral immunotherapy (OIT) for peanut, milk, and egg allergy has emerged as the most clinically advanced form of active treatment. Palforzia (AR101), a standardized peanut OIT, received FDA and EMA approval and represents the first approved pharmaceutical for food allergy treatment. [6] Adjunctive omalizumab (anti-IgE) combined with OIT was efficacious in accelerating desensitization and reducing adverse reactions (1.6% of doses), according to a landmark 2023 systematic review. [6] Sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT) are under active development; Viaskin Peanut patch received regulatory attention. [6] The field is transitioning from desensitization to the goal of sustained unresponsiveness—ideally, true clinical tolerance. Early introduction of allergenic foods—particularly peanut in high-risk infants with eczema or egg allergy—remains the most effective primary prevention strategy, supported by landmark trials such as LEAP. [1]

6.3 Dietary Management of Intolerances

The cornerstone of managing food intolerances is identifying the threshold dose at which symptoms are triggered and personalizing the diet accordingly, rather than instituting blanket elimination. [10] A scientific and reasonable dietary approach can substantially alleviate the clinical symptoms of lactose intolerance; total dairy elimination is rarely necessary. [42] The low-FODMAP diet should be implemented under dietitian supervision and should not be maintained beyond the restriction phase without systematic reintroduction to preserve microbiome diversity. [8] The gluten-free diet remains the definitive management for celiac disease; periodic dietary counselling, micronutrient monitoring (particularly iron, calcium, folate, and B12), and GFD adherence assessment are all required components of long-term care. [29]

7. QUALITY OF LIFE, PSYCHOLOGICAL BURDEN, AND HEALTH EQUITY

Food allergy and intolerance exact a substantial psychosocial toll that is often underestimated in clinical practice. [5] Food allergies significantly reduce children's quality of life; age, number of allergens, and allergy severity are key determinants of

impact. [5] Affected children experience higher levels of anxiety, depression, and reduced psychosocial functioning. [5] Caregivers face constant concerns about accidental exposure, limitations in social activities, financial strain, and increased work absences. [5]

Significant health disparities exist in the diagnosis and management of food allergy. Racial and ethnic minority groups, lower-income families, and Medicaid-enrolled populations face barriers including delayed diagnosis, reduced access to specialist care, and lower rates of epinephrine auto-injector prescription. [3] Racial differences in the timing of food allergen introduction and divergent sensitization patterns linked to geographic pollen exposures further compound these disparities. [3] Addressing health disparities in food allergy requires structural interventions at the levels of clinical training, policy, and patient advocacy. [3]

8. CONCLUSIONS AND RESEARCH PRIORITIES

This systematic review confirms that adverse reactions to food constitute a spectrum ranging from life-threatening IgE-mediated food allergy to prevalent non-immune intolerances, each requiring a distinct diagnostic and therapeutic approach. [1][8]

Several overarching conclusions emerge from the synthesized literature:

- **Mechanistic clarity is essential.** The immune-mediated versus non-immune distinction guides appropriate investigation and avoids both under-treatment (missing true allergy) and over-treatment (unnecessary restriction in intolerance). [10]
- **Validated diagnostics must be prioritized.** The oral food challenge remains the gold standard for allergy; breath testing for carbohydrate intolerances; and tTG-IgA with duodenal biopsy for celiac disease. Commercial IgG panel tests must be actively discouraged. [10][35]
- **Prevalence is rising globally.** Food allergy now affects ~8–10% of the population in industrialized countries; environmental and microbiome factors are prime suspects in driving this trend. [1][6]
- **Immunotherapy is transforming treatment.** OIT for peanut and other allergens, supported by omalizumab, represents the most significant therapeutic advance in decades. [6]
- **Early introduction prevents allergy.** Strategic early introduction of allergenic foods in at-risk infants remains the most powerful primary prevention tool available. [1]
- **Research gaps persist.** NCGS biomarkers, the role of the gut microbiome in modulating allergy severity, long-term safety of immunotherapy, and mechanisms of histamine intolerance remain priority research areas. [7][9][36]

Multidisciplinary care—uniting allergists, gastroenterologists, dietitians, immunologists, and primary care physicians—remains the optimal model for managing this complex and expanding field. Patients deserve evidence-based, personalized dietary guidance that minimizes both allergic risk and unnecessary restriction.[5][8]

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