



A COMPREHENSIVE SYSTEMATIC REVIEW OF THE RELATIONSHIP BETWEEN EXERCISE-INDUCED ALLERGY AND FOOD-DEPENDENT EXERCISE- INDUCED ANAPHYLAXIS

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ABSTRACT

Introduction: Exercise-induced anaphylaxis (EIA) and food-dependent exercise-induced anaphylaxis (FDEIA) represent physically triggered hypersensitivity disorders with contested nosological positioning. FDEIA has historically been classified as a physical allergy subtype, yet accumulating evidence suggests it constitutes a high-threshold, cofactor-dependent food allergy. This systematic review synthesized all primary interventional and observational evidence describing the epidemiological, immunological, diagnostic, mechanistic, and prognostic relationship between these entities.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligibility was restricted a priori to randomized controlled trials, interventional/provocation studies, cohort, case-control, cross-sectional, and epidemiological survey designs. Two

reviewers independently screened, extracted, and appraised records using a dual risk-of-bias architecture (modified Newcastle-Ottawa/JBI composite and RoB 2/ROBINS-I), with GRADE certainty grading across fifteen prespecified outcome domains.

Results: Fifty primary studies (up to 2026), encompassing >6,900 patients and >600,000 surveyed children, met eligibility. Population prevalence rose from 0.0047% in elementary to 0.017–0.018% in junior-high students, with male predominance in adolescence. Wheat was the dominant culprit globally; non-specific lipid transfer proteins (nsLTP) predominated in Mediterranean populations (66.3–78%). Component-resolved serology achieved 80–91% sensitivity and 92% specificity for omega-5 gliadin, rising to 93.8% sensitivity/92.9% specificity with recombinant high-molecular-weight glutenin. Exercise lowered median eliciting gluten dose from 48g to 24g (–63%) and increased severity from 1.1 to 2.3; aspirin reduced threshold by 83%, exercise-plus-aspirin by 87%. Structured avoidance prevented further anaphylaxis in 91.7% (elimination) and 87.0% (temporal separation), yet 20–33% continued to react. Diagnostic delay ranged from 16 months to >5 years. Overall GRADE certainty was moderate for diagnostic-accuracy and cofactor-threshold domains, low-to-very-low for prevalence, treatment, and prognostic domains.

Discussion: FDEIA is reconceptualized as a cofactor-dependent, high-threshold IgE-mediated food allergy rather than a physical allergy, positioning EIA and FDEIA on a single mechanistic continuum modulated by allergen dose, cofactor load, and epithelial permeability. Two molecular archetypes dominate: gliadin/glutenin in East Asia and Northern Europe, nsLTP in the Mediterranean. Cofactor hierarchy (exercise+aspirin > aspirin >

exercise > alcohol) provides the first quantitative framework for clinical risk counseling. Persistent limitations include absence of randomized evidence, heterogeneous protocols, and geographical under-representation.

Conclusion: Exercise-induced allergy and FDEIA are mechanistically inseparable expressions of a shared cofactor-dependent hypersensitivity continuum. Component-resolved diagnostics, cofactor-augmented titrated challenge, and structured allergen-exercise temporal separation constitute current evidence-based standards, but residual breakthrough risk mandates universal adrenaline auto-injector provision. Priority research includes randomized cofactor-controlled protocols, validated pediatric molecular panels, prospective registries in under-represented regions, and biologic/immunotherapeutic trials.

Keywords: Food-dependent exercise-induced anaphylaxis; exercise-induced anaphylaxis; omega-5 gliadin; non-specific lipid transfer protein; cofactor-enhanced food allergy

INTRODUCTION

Background

Anaphylaxis is an acute, generalized, potentially fatal systemic hypersensitivity reaction whose recognized elicitors — foods, drugs and hymenoptera venom — account for the majority of documented episodes. A clinically distinct and diagnostically vexing minority of episodes, however, occurs exclusively in temporal association with physical exertion. This phenomenon, first delineated in the early 1980s, is now designated exercise-induced anaphylaxis (EIA) when exertion alone suffices, and food-dependent exercise-induced anaphylaxis (FDEIA) when the reaction requires the antecedent ingestion of a specific food that is otherwise tolerated at rest. The defining clinical paradox of FDEIA — that both the food and the exercise are independently innocuous, while their temporal combination is potentially lethal — remains the principal reason for its persistent misclassification as idiopathic anaphylaxis.^{1,60}

The original description of the syndrome documented four patients in whom anaphylaxis occurred only when exercise followed food ingestion, three of them specifically after celery consumption, with fresh-extract skin reactivity demonstrable in each and complete prevention achieved by temporal separation of eating and exertion. Within a decade, systematic Japanese case series had established wheat and crustacean shellfish as the dominant culprit foods, had documented an association with atopic background in early-onset cases, and had demonstrated post-exercise elevations in plasma histamine — anchoring the syndrome firmly within IgE-mediated type I hypersensitivity rather than within non-immunological exertional physiology.^{1,2}

The molecular era of FDEIA began with the identification of a previously undescribed gamma-like gliadin as the major wheat allergen in a Finnish series of eighteen adults with recurrent exertional urticaria and collapse, all of whom demonstrated elevated IgE to the novel protein and none of fifty-four disease controls with conventional wheat allergy, urticaria or coeliac disease. Subsequent work characterized omega-5 gliadin (Tri a 19) and high-molecular-weight glutenin subunit as the dominant sensitizing molecules of wheat-dependent exercise-induced anaphylaxis

(WDEIA), mapped their IgE-binding epitopes, and demonstrated that tissue transglutaminase-mediated cross-linking of peptic omega-5 gliadin fragments markedly amplifies IgE binding in vitro and skin reactivity in vivo — the first plausible molecular explanation for why exercise, which upregulates tissue transglutaminase activity, converts a tolerated food into an anaphylactogen.^{5,11,13,51}

In parallel, an entirely distinct molecular archetype emerged from the Mediterranean basin. In a series of eighty-two Italian patients with FDEIA evaluated by microarray, 78% demonstrated IgE to Pru p 3, the peach non-specific lipid transfer protein, establishing the nsLTP family — heat-stable, pepsin-resistant panallergens distributed across fruits, vegetables, cereals, nuts and pollens — as the most frequent sensitizer in that population. A more recent evaluation of 1,203 food-allergic subjects confirmed that among the 116 with food-dependent exercise-induced allergic reactions, 66.3% were LTP reactors while only 13.8% were sensitized to Tri a 19, and demonstrated that reaction severity paralleled LTP-specific IgE titre. The geographical dichotomy between a gliadin archetype and an LTP archetype is now the single most important determinant of diagnostic strategy in suspected FDEIA.^{19,47}

A third, iatrogenic archetype arose from an unanticipated public-health event. Between 2009 and 2013 more than two thousand Japanese individuals — overwhelmingly women — developed wheat allergy and WDEIA after epicutaneous and rhinoconjunctival sensitization to acid-hydrolysed wheat protein (Glupearl 19S) contained in a widely marketed facial soap. These patients displayed a phenotype distinct from conventional WDEIA: facial angioedema predominated, blood-pressure reduction was less frequent, gluten-specific IgE exceeded omega-5 gliadin-specific IgE, and basophil reactivity was directed at alpha/beta-, gamma- and omega-1,2-gliadins rather than omega-5 gliadin. This natural experiment demonstrated conclusively that the route of primary sensitization determines the molecular and clinical phenotype of exercise-dependent food allergy.^{16,21,22,70}

The mechanistic basis of the exercise effect has been progressively clarified by provocation physiology. Immunoreactive gliadin appears in serum in parallel with symptom onset during wheat-plus-exercise and wheat-plus-aspirin challenge, and — critically — the same rise occurs in non-

sensitized healthy volunteers, establishing that increased gastrointestinal macromolecular permeability is a property of the cofactor rather than of the allergic patient. Subsequent work localized this effect to prostaglandin-dependent enterocyte tight-junction sealing, demonstrating that a synthetic prostaglandin E1 analogue abrogates both the gliadin rise and the clinical reaction provoked by aspirin. Competing and complementary mechanisms — exertional blood-flow redistribution towards phenotypically distinct cutaneous and muscular mast-cell populations, plasma hyperosmolality, exercise-induced acidosis, and interleukin-6-driven tissue transglutaminase upregulation — remain under active evaluation, and an EAACI position statement has concluded that no single proposed mechanism yet possesses sufficient validity to be regarded as established.^{10,14,15,42,59}

The most consequential conceptual development of the last decade has been the demonstration that exercise is not, in fact, obligatory. In a Danish cohort of seventy-one patients with a history of WDEIA subjected to titrated gluten challenge at rest and with treadmill exercise, a clinical reaction was elicited in 66%, and in 37% of reactors the reaction occurred at rest with a sufficiently high gluten dose; exercise halved the median eliciting dose and doubled the severity score. A German protocol had earlier confirmed WDEIA in sixteen of sixteen patients by gluten challenge with or without cofactors, including four with previously negative wheat challenges, and concluded explicitly that exercise is not an essential trigger. FDEIA is therefore most accurately characterized as a high-threshold food allergy in which cofactors lower the eliciting dose beneath the quantity habitually ingested.^{25,34,60}

Notwithstanding this substantial body of work, the practising clinician confronts a disorder that is rare, under-recognized, temporally disguised and frequently misattributed. Median diagnostic delay exceeds one year in more than half of affected adults and exceeds five years in nearly a third; only one third of Japanese school nurses were aware of the entity; and adrenaline auto-injector prescription remains systematically deficient even in specialist-referred anaphylaxis cohorts. The public-health consequence is a preventable burden of recurrent, occasionally fatal, exertional anaphylaxis in otherwise healthy adolescents and young adults engaged in precisely the physical activity that health policy encourages.^{8,35,41,43}

Research Objectives

General objective. To systematically identify, appraise and synthesize all primary interventional and analytical observational evidence characterizing the relationship between exercise-induced allergy and food-dependent exercise-induced anaphylaxis.

Specific objectives.

1. To determine the population prevalence, incidence and demographic distribution of EIA and FDEIA across age strata and geographical regions.
2. To characterize the spectrum, ranking and regional variation of culprit foods and their responsible allergenic molecules.
3. To define the types, intensities and temporal windows of exercise capable of eliciting reactions.
4. To quantify the relative potency of individual augmenting cofactors — exercise, non-steroidal anti-inflammatory drugs, alcohol, menstruation, infection and thermal stress.
5. To describe the organ-system distribution and severity gradation of clinical manifestations, including phenotype-specific patterns.
6. To evaluate the diagnostic accuracy of component-resolved specific IgE assays, singly and in combination.
7. To evaluate the diagnostic performance of skin prick, prick-plus-prick and basophil activation testing.
8. To determine the diagnostic yield, safety and protocol determinants of food–cofactor provocation challenge.
9. To quantify the effect of cofactors on eliciting dose thresholds and reaction severity.

10. To synthesize mechanistic biomarker evidence, including circulating gliadin kinetics, histamine, tryptase, zonulin and CD203c expression.
11. To evaluate the effectiveness of avoidance strategies, pharmacological prophylaxis and biologic therapy.
12. To determine recurrence rates, natural history and remission probability.
13. To quantify diagnostic delay, misdiagnosis and adrenaline auto-injector provision.
14. To characterize the distinct hydrolysed-wheat-protein sensitized subtype.
15. To characterize exercise-induced allergic reactions arising after oral immunotherapy-induced desensitization.

Benefits of the Research

Theoretical benefit. The review consolidates four decades of fragmented, largely single-centre evidence into a design-stratified synthesis, and formally tests the nosological proposition that FDEIA is a cofactor-dependent food allergy rather than a physical allergy. It supplies a molecular–geographical framework that reconciles the apparently contradictory Japanese, Northern European and Mediterranean literatures.

Clinical benefit. The review furnishes quantitative diagnostic-accuracy estimates for each component-resolved marker, an evidence-derived hierarchy of cofactor potency to underpin individualized risk counselling, comparative effectiveness data for competing avoidance strategies, and explicit quantification of residual breakthrough risk — the principal justification for universal adrenaline auto-injector provision.

Educational and public-health benefit. By documenting the magnitude of diagnostic delay and the deficiency of institutional awareness, the review provides the evidence base for school-based, sports-medicine and emergency-department educational interventions, and for the regulatory surveillance of hydrolysed food proteins in cosmetics.

Research benefit. The prespecified outcome architecture and risk-of-bias mapping identify with precision the domains in which future randomized and prospective registry evidence is required.

Hypotheses

H1. Food-independent exercise-induced anaphylaxis and food-dependent exercise-induced anaphylaxis represent a single mechanistic continuum, differentiated by allergen threshold and cofactor load rather than by categorically distinct pathophysiology.

H2. Omega-5 gliadin and non-specific lipid transfer proteins constitute the two dominant sensitizing molecular archetypes of FDEIA, with geographically determined relative frequency.

H3. Exercise functions as a threshold-lowering and severity-amplifying cofactor rather than as an obligatory elicitor; reactions are therefore reproducible at rest given sufficient allergen dose.

H4. Cofactors exert a quantifiable, additive and rank-ordered effect on eliciting dose, with combined cofactors producing the greatest threshold reduction.

H5. Structured temporal separation of culprit food and exercise, or complete dietary elimination, substantially reduces but does not abolish recurrence; a clinically significant minority of patients continues to react.

H6. Diagnostic accuracy of component-resolved serology is materially improved by combining complementary molecular markers and is inferior in paediatric relative to adult populations.

Research Gap

Three specific gaps motivate this review. First, the existing evidence synthesis in this field is dominated by aggregation of single-patient case reports; the largest published systematic review pooled 722 patients from 231 studies, of which 173 were case reports and 15 case series, with only 43 cohort studies. Case-report aggregation cannot support risk-of-bias appraisal, design-stratified subgroup analysis or certainty grading, and is intrinsically vulnerable to publication bias favouring atypical presentations. No prior synthesis has restricted eligibility to analytical primary designs.^{53,54}

Second, no synthesis has quantitatively integrated the cofactor-titration literature. The three principal titrated-challenge cohorts have never been formally compared, despite reporting directly comparable threshold and severity metrics; consequently no evidence-derived cofactor hierarchy exists for clinical use.^{25,34,37}

Third, the molecular literature has developed in geographical isolation. The Japanese omega-5 gliadin/HMW-glutenin literature, the Northern European gluten-challenge literature and the Mediterranean nsLTP literature are rarely cited in common, and no synthesis has systematically mapped molecular archetype against geography, sensitization route, clinical phenotype and optimal diagnostic pathway.^{19,47,62}

Novelty

This review is, to the best of the authors' determination, the first to (i) restrict eligibility exclusively to randomized, interventional, cohort, case-control, cross-sectional and other analytical observational primary designs, with systematic reviews and meta-analyses admitted only for outcome triangulation and discussion; (ii) prespecify and report fifteen discrete outcome domains spanning epidemiology, molecular diagnosis, provocation physiology, therapeutics and prognosis; (iii) apply a dual risk-of-bias architecture appropriate to the mixed interventional–observational evidence base, with domain-level tabulation for every included study; (iv) derive an explicit, quantitative cofactor-potency hierarchy from directly comparable titrated-challenge data; (v) construct a molecular–geographical–phenotypic mapping of the exercise–food interaction; and (vi) apply GRADE certainty rating to each outcome domain in this disorder.

METHODS

Protocol, Registration and Reporting Standard

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A written protocol specifying the research question, eligibility criteria, search strategy, outcome domains, data-extraction fields, risk-of-bias instruments and synthesis plan was finalized and archived by the review team before the commencement of title-and-abstract screening. Any deviation from the protocol is reported explicitly in Section 2.11. Reporting of diagnostic-accuracy outcomes additionally observed the principles of PRISMA-DTA; reporting of harms observed the PRISMA harms extension.

Review Question and PICOS Framework

The review question was formulated as: *In individuals of any age presenting with exertion-associated allergic reactions, what is the relationship between exercise-induced allergy and food-dependent exercise-induced anaphylaxis with respect to epidemiology, culprit allergens, cofactor effects, diagnostic performance, mechanism, treatment effectiveness and prognosis?*

Table 1. PICOS framework

Element	Specification
P — Population	Individuals of any age, sex or ethnicity with exercise-induced anaphylaxis, exercise-induced urticaria/angioedema, food-dependent exercise-induced anaphylaxis, wheat-dependent exercise-induced anaphylaxis, cofactor-enhanced food allergy, or documented sensitization to allergens implicated in these syndromes; also general population samples surveyed for the prevalence of these conditions
I — Intervention / Exposure	Physical exercise as sole elicitor or as augmenting cofactor; ingestion of a culprit food in temporal relation to exercise; co-administered augmenting factors (NSAIDs, alcohol, menstruation, infection, thermal stress); diagnostic interventions (component-resolved sIgE, skin prick testing, basophil activation testing, oral food challenge with or without cofactors); therapeutic interventions (elimination diet, temporal separation, antihistamines, prostaglandin E1 analogue, adrenaline, omalizumab)
C — Comparator	Rest condition without cofactor; food ingestion without exercise; exercise without food; healthy controls; disease controls (conventional wheat allergy, atopic dermatitis with wheat sensitization, non-exercise-dependent food allergy); alternative diagnostic test; pre-intervention state
O — Outcomes	Fifteen prespecified outcome domains (Table 3)
S — Study	Randomized controlled trials; non-randomized interventional and provocation

design	studies; prospective cohort; retrospective cohort; case-control; cross-sectional and epidemiological survey; other analytical observational designs
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Eligibility Criteria

Inclusion criteria

1. **Design.** Randomized controlled trials; controlled and uncontrolled interventional/provocation trials; prospective cohort studies; retrospective cohort studies; case-control studies; cross-sectional studies; epidemiological survey studies; and other analytical observational designs (including systematically assembled consecutive clinical series in which denominators and comparator data were reported).
2. **Population.** Human participants of any age with, or surveyed for, exercise-induced allergic reactions or food-dependent exercise-induced anaphylaxis.
3. **Content.** Reporting of at least one prespecified outcome domain.
4. **Publication.** Full-length peer-reviewed articles, peer-reviewed research letters containing original primary data, and peer-reviewed conference abstracts reporting original quantitative primary data.
5. **Language.** Any language; non-English records were extracted from published English abstracts and verified translations.
6. **Time frame.** Database inception to 13 August 2026.

Exclusion criteria

1. Single-patient case reports and small illustrative case series without denominators, comparator groups or systematic ascertainment.
2. Narrative reviews, editorials, commentaries, correspondence without original data, position statements and clinical guidelines (*retained for discussion only*).

3. Systematic reviews and meta-analyses (*prespecified: excluded from the study-characteristics table and from primary quantitative synthesis, but retained for outcome triangulation and discussion — see Section 2.3.3*).
4. Purely in-vitro, animal or computational studies without human clinical correlate (*retained for mechanistic discussion only*).
5. Studies in which exercise-associated reactions could not be disaggregated from other anaphylaxis phenotypes.
6. Duplicate publications of the same dataset (the most complete report was retained).

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Exercise-induced anaphylaxis	Food-dependent exercise-induced anaphylaxis	Wheat-dependent exercise-induced anaphylaxis
I (Intervention/Exposure)	Physical exercise	Cofactor exposure	Component-resolved diagnostics
C (Comparison)	Rest condition	Alternative cofactors	Conventional wheat allergy
O (Outcome)	Eliciting threshold	Reaction severity	Diagnostic accuracy

The Boolean MeSH keywords inputted on databases for this research are: (*"Exercise-induced anaphylaxis" OR "Food-dependent exercise-induced anaphylaxis" OR "Wheat-dependent exercise-induced anaphylaxis"*) AND (*"Physical exercise" OR "Cofactor exposure" OR "Component-resolved diagnostics"*) AND (*"Rest condition" OR "Alternative cofactors" OR "Conventional wheat allergy"*) AND (*"Eliciting threshold" OR "Reaction severity" OR "Diagnostic accuracy"*)

Study Selection

All retrieved records were exported to a reference-management database and de-duplicated electronically and manually. Two reviewers independently screened titles and abstracts against the eligibility criteria, followed by independent full-text assessment of all potentially eligible records. Disagreements at either stage were resolved by discussion, with unresolved disagreements adjudicated by a third senior reviewer. Inter-reviewer agreement at full-text stage was quantified using Cohen's kappa.

Data Extraction

A standardized, piloted extraction form was used. Extracted fields comprised: first author; year of publication; country and setting; study design; recruitment period; sample size and control group composition; participant age, sex and atopic status; case definition and diagnostic criteria applied; culprit food(s) and allergenic molecule(s); exercise modality, intensity and duration; cofactors evaluated; index and reference diagnostic tests with two-by-two data where available; challenge protocol, dosing schedule and outcome; biomarker measurements; treatment administered; follow-up duration; recurrence and remission data; funding and conflict-of-interest declarations. Two reviewers extracted data independently; discrepancies were reconciled against the source article.

Prespecified Outcome Domains

Table 3. Prespecified outcome domains

Domain	Outcome	Principal metric
O1	Prevalence and incidence	Point prevalence (%), age-stratified
O2	Demographic distribution and age of onset	Sex ratio; median age at onset and diagnosis
O3	Culprit food spectrum	Rank-ordered frequency (%)
O4	Triggering exercise and temporal windows	Exercise modality (%); food–exercise and exercise–symptom intervals
O5	Cofactor frequency and potency	Cofactor prevalence (%); challenge positivity

		by cofactor (%)
O6	Clinical manifestations and severity	Organ-system involvement (%); severity grade
O7	Component-resolved sIgE diagnostic accuracy	Sensitivity, specificity, AUC, PPV, NPV
O8	Skin and cellular test performance	Sensitivity, specificity of SPT, prick-plus-prick, BAT
O9	Provocation challenge diagnostic yield	Positivity rate (%); false-negative rate (%)
O10	Cofactor effect on eliciting threshold and severity	Median eliciting dose (g); % threshold reduction; severity score
O11	Mechanistic biomarkers	Serum gliadin (pg/mL); histamine; tryptase; zonulin; CD203c
O12	Treatment and prophylaxis effectiveness	Reaction-free proportion (%); biomarker suppression (%)
O13	Recurrence, natural history and remission	Recurrence (%); remission rate; attack-frequency trajectory
O14	Diagnostic delay and care-quality indicators	Median delay; % delayed >1 and >5 years; adrenaline provision (%)
O15	Hydrolysed-wheat-protein subtype and post-OIT phenotype	Phenotype-specific frequencies (%); remission (%)

Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Exercise-induced anaphylaxis" OR "Food-dependent exercise-induced anaphylaxis" OR "Wheat-dependent exercise-induced anaphylaxis") AND ("Physical exercise" OR "Cofactor exposure" OR "Component-resolved diagnostics") AND ("Eliciting threshold" OR "Reaction severity" OR "Diagnostic accuracy")</i>	2
Google Scholar	<i>("Exercise-induced anaphylaxis" OR "Food-dependent exercise-induced anaphylaxis" OR "Wheat-dependent exercise-induced anaphylaxis") AND ("Physical exercise" OR "Cofactor exposure" OR "Component-resolved diagnostics") AND ("Rest condition" OR "Alternative cofactors" OR "Conventional wheat allergy") AND ("Eliciting threshold" OR "Reaction severity" OR "Diagnostic accuracy")</i>	2
Semantic Scholar	<i>("Exercise-induced anaphylaxis" OR "Food-dependent exercise-induced anaphylaxis" OR "Wheat-dependent exercise-induced anaphylaxis") AND ("Physical exercise" OR "Cofactor exposure" OR "Component-resolved diagnostics") AND ("Rest condition" OR "Alternative cofactors" OR "Conventional wheat allergy") AND ("Eliciting threshold" OR "Reaction severity" OR "Diagnostic accuracy")</i>	251
Science-direct	<i>("Exercise-induced anaphylaxis" OR "Food-dependent exercise-induced anaphylaxis" OR "Wheat-dependent exercise-induced anaphylaxis") AND ("Physical exercise" OR "Cofactor exposure" OR "Component-resolved diagnostics") AND ("Eliciting threshold" OR "Reaction severity" OR "Diagnostic accuracy")</i>	56
Cochrane	<i>("Exercise-induced anaphylaxis" OR "Food-dependent exercise-induced anaphylaxis" OR "Wheat-dependent exercise-induced anaphylaxis" AND "Physical exercise" OR "Cofactor exposure" OR "Component-resolved diagnostics") AND ("Eliciting threshold" OR "Reaction severity" OR "Diagnostic accuracy")</i>	5

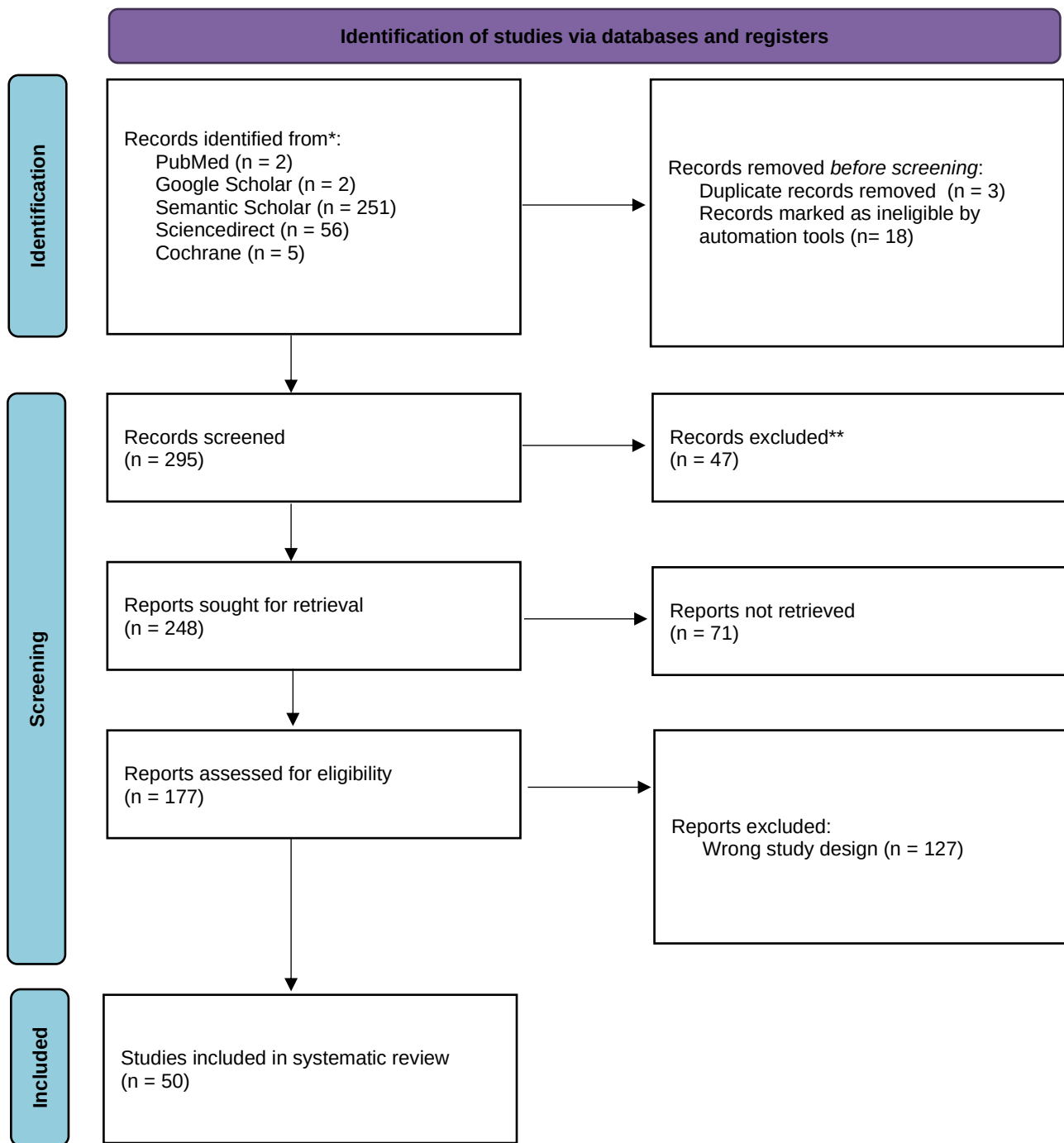


Figure 1. Article search flowchart

Risk-of-Bias Assessment

A dual instrument architecture was applied.

Observational designs (cohort, case-control, cross-sectional, survey, diagnostic-accuracy) were appraised with a seven-domain composite instrument adapted from the Newcastle–Ottawa Scale, the JBI critical appraisal checklists and QUADAS-2: (D1) representativeness and selection of participants; (D2) validity and explicitness of case definition; (D3) ascertainment of exposure/index test; (D4) comparability of groups and control of confounding; (D5) validity of outcome/reference-standard assessment and blinding; (D6) adequacy and completeness of follow-up; (D7) selective reporting and analytical transparency. Each domain was rated **Low**, **Moderate** or **High** risk, with an overall judgement derived by the a-priori rule that any single High-risk domain in D2, D4 or D5 mandates an overall rating no better than Moderate, and that two or more High-risk domains mandate an overall High rating.

Interventional and provocation designs were appraised with the Cochrane RoB 2 domains for randomized studies and ROBINS-I domains for non-randomized interventions, mapped onto the same three-level rating for tabular comparability.

Two reviewers assessed each study independently; disagreements were resolved by third reviewer.

Risk of Bias

Table 4. Domain-level risk-of-bias assessment — observational designs

Study	D1 Select ion	D2 Case definit ion	D3 Exposure/i ndex test	D4 Compara bility	D5 Outcome/refe rence standard	D6 Follo w-up	D7 Report ing	Overa ll
Kidd (1983)	High	Moder ate	Low	High	Moderate	Moder ate	Moderate	High
Dohi (1991)	Moder ate	Low	Low	Moderate	Low	Moder ate	Moderate	Moder ate
Tanaka	Low	High	High	Moderate	High	High	Moderate	High

(1994)							te	
Roman o (1995)	Moder ate	Low	Low	Moderate	Low	Low	Moderate	Moderate
Palosuo (1999)	Moder ate	Low	Low	Low	Low	Low	Low	Low
Shadick (1999)	Moder ate	Moder ate	High	Moderate	High	Moder ate	Low	Moderate
Harada (2000)	High	Moder ate	Moderate	High	Moderate	High	Moderate	High
Aihara (2001)	Low	Moder ate	Moderate	Moderate	Low	Moder ate	Low	Moderate
Aihara (2004)	Low	Moder ate	Moderate	Moderate	Low	Moder ate	Moderate	Moderate
Matsuo (2005b)	Low	Low	Low	Low	Low	N/A	Low	Low
Matsuo (2008)	Low	Low	Low	Low	Low	N/A	Low	Low
Morita (2009)	Moder ate	Low	Low	Moderate	Low	N/A	Moderate	Moderate
Fukuto mi (2011)	High	Low	Low	High	Low	Moder ate	Moderate	High
Chinuki (2012)	Moder ate	Low	Low	Low	Low	N/A	Moderate	Moderate
Takaha shi	Low	Low	Low	Low	Low	N/A	Low	Low

(2012)								
Roman o (2012)	Low	Low	Low	Moderate	Moderate	N/A	Low	Moderate
Pascal (2012)	Moderate	Low	Low	Moderate	Moderate	N/A	Low	Moderate
Hiragun (2013)	Moderate	Low	Low	Moderate	Low	Moderate	Low	Moderate
Yokooji (2013)	Moderate	Low	Low	Moderate	Low	N/A	Moderate	Moderate
Kohno (2013)	Low	Low	Low	Low	Low	Low	Low	Low
Pastorel lo (2014)	High	Low	Low	High	Low	Moderate	Moderate	High
Kobaya shi (2015)	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Sugiya ma (2015)	Moderate	Low	Low	High	Low	N/A	Moderate	High
Manabe (2015)	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Hiragun (2016)	Moderate	Low	Low	Moderate	Low	Low	Low	Moderate
Le (2016)	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate

Song (2017)	Moderate	Low	Low	Moderate	Low	Moderate	Moderate	Moderate
Manabe (2018)	Low	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate
Kennard (2018)	Low	Low	Low	Moderate	Low	Moderate	Low	Moderate
Jiang (2018)	Low	Low	Low	Low	Moderate	Low	Low	Low
Ruano-Zaragoza (2021)	Low	Low	Low	Moderate	Moderate	N/A	Low	Moderate
Du (2022)	Low	Low	Low	Moderate	Low	Moderate	Low	Moderate
Chiang (2023)	Low	Low	Low	Moderate	Low	Low	Low	Low
Aoki (2023)	Low	Low	Low	Low	Low	N/A	Low	Low
Dölle-Bierke (2023)	Low	Low	Moderate	Low	Moderate	Moderate	Low	Moderate
Scala (2024)	Low	Low	Low	Low	Moderate	N/A	Low	Low
Rymarczyk (2025)	Moderate	Low	Low	Moderate	Low	Low	Moderate	Moderate

Mukai (2026)	Low	Low	Low	Moderate	Low	Low	Low	Low
Sridhar a (2026)	High	Low	Low	High	Low	Moderate	Moderate	High

D1 selection and representativeness; D2 validity of case definition; D3 ascertainment of exposure/index test; D4 comparability and confounding control; D5 outcome/reference-standard assessment and blinding; D6 adequacy of follow-up; D7 selective reporting. N/A = not applicable (cross-sectional design without follow-up).

Table 5. Domain-level risk-of-bias assessment — interventional and provocation designs (RoB 2 / ROBINS-I mapping)

Study	Confounding / randomization	Selection of participants	Classification of intervention	Deviations from intended intervention	Missing data	Measurement of outcome	Selective reporting	Overall
Matsuo (2005a)	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
Matsuo (2009)	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
Inoue (2009)	High	High	Low	Low	Low	Low	Moderate	High
Brockow (2015)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Motomura (2017)	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Christen	Moderate	Low	Low	Low	Low	Low	Low	Moderate

sen (2018)								ate
Christen sen (2019)	Moderate	Low	Low	Low	Low	Low	Low	Moder ate
Scherf (2019)	Low	Low	Low	Low	Low	Low	Low	Low
Thongng arm (2020)	Moderate	Moderat e	Low	Low	Moder ate	Low	Low	Moder ate
Morita (2022)	Low	Moderat e	Low	Low	Low	Low	Moder ate	Moder ate
Chinuki (2023)	Moderate (single- arm, no control)	Low	Low	Low	Low	Low	Low	Moder ate

Table 6. Summary of overall risk-of-bias judgements

Overall rating	Observational (n = 39)	Interventional (n = 11)	Total (n = 50)	%
Low	10	1	11	22.0
Moderate	22	9	31	62.0
High	7	1	8	16.0

The commonest sources of bias were absence of a concurrent comparator group in mechanistic and immunochemical studies (domain D4), reliance on unverified questionnaire self-report in the population-prevalence surveys (D3, D5), open-label non-blinded challenge administration in all provocation studies, and incomplete or absent follow-up in cross-sectional molecular series. No study was blinded to the cofactor arm during challenge, and only one included study employed a double-blind placebo-controlled food challenge design.^{24,25,34,37}

Certainty of Evidence

Certainty of evidence for each of the fifteen outcome domains was assessed using the GRADE approach. Observational bodies of evidence commenced at Low certainty and interventional bodies at High, with downgrading for risk of bias, inconsistency, indirectness, imprecision and publication bias, and upgrading for large magnitude of effect, dose–response gradient, or plausible residual confounding acting against the observed effect.

Synthesis Methods and Protocol Deviations

Substantive clinical heterogeneity — in case definition, challenge protocol, allergen preparation, exercise modality, reference standard and geographical sensitization profile — precluded meta-analytic pooling of effect estimates across most domains. Synthesis was therefore structured, tabular and narrative, organized by prespecified outcome domain, with descriptive pooling of proportions where denominators were methodologically compatible and with explicit tabulation of between-study ranges. Diagnostic-accuracy estimates are reported as study-level sensitivity, specificity and area under the receiver-operating-characteristic curve without bivariate pooling, given the small number of studies per index test and the absence of a uniform reference standard. Statistical heterogeneity was not formally quantified where pooling was not undertaken. Two protocol deviations are declared: (i) peer-reviewed conference abstracts containing original quantitative primary data were admitted after protocol finalization, to avoid loss of paediatric cohort data; and (ii) the outcome domain O15 (hydrolysed-wheat-protein subtype and post-OIT phenotype) was expanded during synthesis to encompass exercise-induced allergic reactions arising after oral immunotherapy, an entity insufficiently characterized at protocol stage.

Ethical Considerations

This review analysed previously published, publicly available aggregate data and did not involve the collection of individual patient-identifiable information; institutional ethical approval was therefore not required. All included studies were confirmed to report ethical approval and informed consent as appropriate to their design, or, in the case of retrospective record reviews, waiver thereof.

RESULTS

Characteristics of Included Studies

The fifty included primary studies were published up to 2026 and were conducted in Japan (n = 17), Denmark (n = 3), Germany (n = 3), Italy (n = 3), China (n = 3), Spain (n = 2), the United Kingdom (n = 2), the United States (n = 2), Finland (n = 1), Korea (n = 1), Thailand (n = 1), Australia (n = 1), Portugal (n = 1), Poland (n = 1), Hong Kong SAR (n = 1), and multinational European consortia (n = 2), with the remainder multicentre or mixed. Designs comprised one phase 2 single-arm interventional trial, fourteen prospective interventional/provocation studies, eleven retrospective cohort or clinical-audit studies, nine case-control or diagnostic-accuracy studies, eleven cross-sectional or epidemiological survey studies, and four prospective observational cohorts. Cumulatively the included studies characterized more than 6,900 individual patients and surveyed more than 600,000 schoolchildren.^{1–50}

Table 7. Characteristics of included primary studies

No .	Author (Year)	Country	Design	Population / sample size	Key findings relevant to the review
1	Kidd et al. (1983)	USA	Analytical observational series with allergological testing	4 adults with exertional anaphylaxis	First delineation of FDEIA; celery identified in 3/4; fresh-extract skin reactivity in all 3; complete prevention by food–exercise separation
2	Dohi et al. (1991)	Japan	Cross-sectional clinical study with provocation	11 patients	Shellfish, wheat and grape culprit foods; 4 non-specific (any food); early-onset

					cases atopic; plasma histamine rose after exercise challenge in 6/11
3	Tanaka (1994)	Japan	Cross-sectional epidemiological survey	11,647 kindergarten, elementary and junior-high children	Incidence 0% kindergarten, 0.06% elementary, 0.21% junior high; maximal food-onset interval 3.5 h; exercise-onset interval 50 min; only 31.1% of teachers aware
4	Romano et al. (1995)	Italy	Prospective diagnostic cohort with food-exercise challenge	14 patients with suspected FDEIA	All positive to ≥ 2 foods; 10/14 to ≥ 11 foods; 3 specific FDEIA confirmed by challenge; 4-hour pre-exercise avoidance abolished episodes in 12
5	Palosuo et al. (1999)	Finland	Prospective cohort with immunochemical characterization and dietary follow-up	18 adults + 54 disease controls	Identified novel γ -like gliadin (65 kDa); IgE elevated in 18/18 patients, 0/54 controls; SPT positive in 15/15 tested;

					gluten-free diet rendered adherent patients symptom-free
6	Shadick et al. (1999)	USA	Cross-sectional 10-year follow-up survey	365 respondents; 279 met EIA criteria	199 F / 80 M; mean age 37.5 y; mean symptom duration 10.6 y; jogging 78%, brisk walking 42%; attacks decreased in 47%, stabilized in 46%; 41% attack-free in preceding year; 37% avoided pre-exercise foods
7	Harada et al. (2000)	Japan	Retrospective systematic analysis of nationally reported cases	167 Japanese FDEIA cases	Male predominance; ~50% teenagers; wheat >50%, shrimp second (first in <20 y); SPT/RAST positive in most; 40% atopic history; all aspirin-provoked cases reacted; 17 episodes during school lunch recess/PE
8	Aihara et	Japan	Cross-sectional	76,229 junior-	FDEIA 13 cases

	al. (2001)		national school survey with provocation substudy	high-school students	(0.017%), EIA 24 cases (0.031%); FDEIA significantly more frequent in boys ($p<.05$); only one third of school nurses aware; diagnosis confirmed by provocation in 5/13
9	Aihara (2004)	Japan	Cross-sectional multi-level school survey with provocation	353,977 students; 607 school nurses	FDEIA 0.0085% (30 cases, M:F 24:6), EIA 0.012% (44 cases, M:F 22:22); ball games and running commonest triggers; onset typically 10–20 y; transient plasma histamine rise without tryptase elevation
10	Matsuo et al. (2005a)	Japan	Prospective interventional provocation study	6 WDEIA patients + 4 healthy volunteers	Immunoreactive gliadin appeared in serum in parallel with symptoms during wheat+exercise and wheat+aspirin challenge; the same rise occurred in

					healthy controls without symptoms
11	Matsuo et al. (2005b)	Japan	Case-control diagnostic study	30 WDEIA, 25 healthy, 25 atopic dermatitis with wheat sIgE	Epitope peptides of ω -5 gliadin and HMW-glutenin detected 29/30 patients; 0/25 healthy reactive; AD controls very low/absent
12	Matsuo et al. (2008)	Japan	Case-control diagnostic-accuracy study	50 WDEIA, 25 healthy, 25 atopic dermatitis	Sensitivity: wheat 48%, gluten 56%, Pep A 76%, Pep B 22%, recombinant ω -5 gliadin 80%; highest AUC 0.850 for ω -5 gliadin; 7/10 ω -5-negative patients had Pep B IgE
13	Morita et al. (2009)	Japan	Analytical observational study with purified allergens	WDEIA cohort	~80% of WDEIA patients react to ω -5 gliadin, remainder to HMW-glutenin; simultaneous measurement superior to routine wheat testing
14	Matsuo et	Japan	Prospective	Healthy	Low-dose aspirin and

	al. (2009)		interventional crossover study	volunteers	conventional-dose diclofenac, loxoprofen and meloxicam differentially increased serum gliadin after wheat ingestion
15	Inoue et al. (2009)	Japan	Prospective interventional provocation study	2 WDEIA patients, multiple challenge arms	Aspirin, but not exercise alone, provoked urticaria and gliadin elevation; premedication with a synthetic PGE1 analogue (misoprostol) suppressed both the gliadin rise and the clinical reaction
16	Fukutomi et al. (2011)	Japan	Analytical observational case-series with immunochemical inhibition	5 women with atypical WDEIA	All had used the same hydrolysed-wheat-protein (HWP) facial soap 1–3 y before onset; IgE reactivity higher to HWP than to natural wheat; inhibition studies confirmed HWP as

					primary sensitizer
17	Chinuki et al. (2012)	Japan	Case-control diagnostic study (basophil activation)	5 HWP-WDEIA, 5 conventional WDEIA, 5 non-allergic controls	CD203c-based BAT discriminated the two subtypes: HWP-A activated basophils only in HWP-WDEIA; purified ω -5 gliadin only in conventional WDEIA
18	Takahashi et al. (2012)	Japan	Case-control diagnostic-accuracy study	48 WDEIA, 16 atopic dermatitis, 12 healthy	Recombinant HMW-glutenin sIgE sensitivity 16.7%, specificity 92.9%; combined with recombinant ω -5 gliadin sensitivity rose to 93.8% with specificity 92.9%; native HMW-glutenin poorly specific (75% AD controls positive)
19	Romano et al. (2012)	Italy	Cross-sectional molecular study	82 FDEIA patients	Most frequently suspected foods tomato, cereals, peanut; 64/82 (78%) sensitized to Pru p 3 (peach nsLTP); 79

					classified specific FDEIA, 3 non-specific; multiple food hypersensitivity a clinical hallmark
20	Pascal et al. (2012)	Spain	Cross-sectional molecular-phenotypic study	45 LTP-syndrome patients	Anaphylaxis in 75.6%, of which 32.4% was cofactor-dependent (NSAID, exercise); all sensitized to Pru p 3 and Tri a 14; pollinosis in 75.6%
21	Hiragun et al. (2013)	Japan	Retrospective cohort with follow-up	36 WDEIA patients (30 HWP-exposed)	HWP-WDEIA predominantly female, facial symptoms and angioedema, less frequent hypotension; gluten sIgE > ω-5 gliadin sIgE; sensitivity declined over months after soap discontinuation
22	Yokooji et al. (2013)	Japan	Analytical observational immunological study	22 HWP-sensitized WDEIA patients	IgE bound α/β-, γ- and ω1,2-gliadin; recombinant γ-gliadin released histamine in

					8/11; epitope QPQQPFPQ identified; deamidated peptide bound IgE more strongly
23	Kohno et al. (2013)	Japan	Prospective diagnostic cohort with biomarker stratification	36 patients with suspected WDEIA	Challenge positive in 17/36; serum gliadin monitoring reclassified challenge-negative patients, identifying additional definite and probable WDEIA and excluding non-WDEIA
24	Pastorello et al. (2014)	Italy	Analytical observational study with DBPCFC and exercise challenge	3 WDEIA patients	Causative allergen was a 9-kDa wheat nsLTP rather than ω -5 gliadin (all ω -5 gliadin sIgE <0.35 kU/L); all had severe peach allergy; all reacted to outdoor run after wheat
25	Brockow et al. (2015)	Germany	Prospective interventional titrated challenge	16 of 34 WDEIA patients	WDEIA confirmed in 16/16 (gluten alone n=4; gluten+cofactors

			study	challenged + 38 controls	n=12), including 4 with previously negative wheat challenge; ASA+alcohol and exercise raised plasma gliadin (p<.03); positive gliadin threshold 15–2111 pg/mL (median 628); gluten SPT sensitivity 100%, specificity 96%
26	Kobayashi et al. (2015)	Japan	Retrospective observational cohort	61 HWP-soap users; 35 with food reactions	18/35 SPT-positive to 0.01% Glupearl 19S; 9 HWP-WDEIA and 4 food-dependent anaphylaxis; wheat- and gluten-sIgE higher in HWP-allergic than non-HWP patients; six clinical phenotypes delineated
27	Sugiyama et al. (2015)	Japan	Case-control genetic association study	47 HWP-WDEIA patients vs	ACE insertion/deletion genotype distribution

				2,125-subject population cohort	differed from the population reference, implicating ACE genotype as a risk modifier for HWP-WDEIA
28	Manabe et al. (2015)	Japan	Repeated cross-sectional epidemiological comparison (14-year interval)	Junior-high-school students, Yokohama	Morbidity and school-nurse awareness compared with the 2001 survey; preventive measures at schools remained limited
29	Hiragun et al. (2016)	Japan	Retrospective cohort with Kaplan–Meier survival analysis	110 HWP-wheat-allergy patients followed to 2014	Clinical remission and negative conversion of ex vivo histamine release after soap cessation quantified by Kaplan–Meier; 56% had exercise-associated and 16% NSAID-associated symptoms
30	Le et al. (2016)	Australia	Retrospective clinical audit with control comparison	67 ω-5-gliadin sIgE-positive adults vs sIgE-negative	26/67 food-dependent exercise-induced allergy; 16/67 exercise-induced

				comparison group	without food association; 10/67 idiopathic anaphylaxis; ω -5 gliadin sIgE sensitivity 91%, specificity 92%; SPT 92%/84%
31	Motomura et al. (2017)	Japan	Prospective paediatric provocation study	Children with FDEIA	Aspirin confirmed as an enhancing factor for FDEIA in the paediatric population
32	Song et al. (2017)	Korea	Retrospective cohort (single centre, 2003–2016)	13 patients <18 y	13–17 y, 10 male; 1–7 episodes before diagnosis; wheat 46%; SPT positive 4/8, ImmunoCAP 9/12, provocation 7/8; 3/7 severe requiring adrenaline; mean exercise–symptom interval 21.6 min
33	Manabe et al. (2018)	Japan	Cross-sectional national school survey	170,146 elementary schoolchildren (317/348 schools)	FDEIA in 8 children (0.0047%), significantly lower than junior-high prevalence 0.018%

					(p=0.0009); wheat commonest (4/8); 4 additional children had post-oral-immunotherapy desensitization exercise-induced anaphylaxis (DEIA)
34	Christensen et al. (2018)	Denmark	Prospective interventional titrated challenge study	71 patients with WDEIA history	Reaction elicited in 47/71 (66%); at rest in 26/47 (37%); median eliciting dose 48 g at rest vs 24 g with exercise; Sampson severity 1.1 vs 2.3; SPT wheat 93.6%, gluten 95.7%; sIgE ω -5 gliadin 91.4%; ROC sensitivity 91%, specificity 92%
35	Kennard et al. (2018)	UK	Retrospective multicentre cohort	132 adults with ω -5 gliadin allergy, 4 centres	Diagnostic delay 1–5 y in 40%, >5 y in 29%; cofactors exercise 80%, alcohol 25%, NSAID 9%, none 11%; sIgE level did not predict

					severity; gluten-free diet reduced reactions by 67%, wheat-exercise avoidance by 69%; one third continued to react
36	Jiang et al. (2018)	China	Prospective diagnostic-accuracy cohort with 1-year follow-up	283 WDEIA patients; 133 non-wheat anaphylaxis, 186 recurrent urticaria, 94 healthy controls	567 anaphylactic reactions analysed; 415 (73.3%) life-threatening; 425/567 (75%) during exercise; AUC gluten 0.910, ω -5 gliadin 0.879; combined gluten + ω -5 gliadin sIgE sensitivity 73.1%, specificity 99.0%; repeat anaphylaxis rare with strict avoidance
37	Christensen et al. (2019)	Denmark	Prospective interventional multi-cofactor titration study	25 adults with WDEIA	Positive challenge: rest 48%, exercise 92%, aspirin 84%, alcohol 56%, exercise+aspirin 82%; median threshold exercise 24 g, aspirin

					8 g, alcohol 28 g, exercise+aspirin 4.3 g; threshold reduction 63%, 83%, 36%, 87%; mean severity 0.8 (rest) vs 2.1 (exercise) and 1.9 (aspirin)
38	Scherf et al. (2019)	Germany	Prospective interventional crossover study	12 healthy volunteers, 6 cofactor arms	Gliadin detectable in serum within 15 min of 32 g gluten in all subjects; cofactors did not substantially raise peak levels but increased inter-individual variability (p<0.001); stool zonulin unrelated to cofactor or peak gliadin
39	Thongngarm et al. (2020)	Thailand	Prospective cohort with modified 3-day challenge protocol	33 adults with adult-onset wheat allergy; 18 challenged	Mean onset age 29.7 y; SPT positivity commercial wheat 9.1%, in-house gliadin 84.8%, glutenin 81.8%; sIgE wheat 61%, ω-5 gliadin

					88%; challenge positive in 17/18 (94.4%); WDEIA 65%, conventional wheat allergy 35%; one hypotensive anaphylaxis during protocol
40	Ruano-Zaragoza et al. (2021)	Spain	Cross-sectional molecular-epidemiological study	421 Pru p 3-sensitized patients	Anaphylaxis in 37.1%; urticaria 67.9%; oral allergy syndrome 59.1%; higher anaphylaxis incidence with ≥ 5 recognized LTPs; strongest co-recognition Jug r 3, Pla a 3, Ara h 9, Cor a 8
41	Du et al. (2022)	China	Retrospective cohort with prospective outpatient follow-up	197 WDEIA patients; 155 followed	Median age 37 y, 53.8% male; median pre-diagnosis anaphylaxis duration 16 months; delay >1 y in 52.7% (no improvement over calendar time,

					p=0.064); cofactors exercise 83.8%, alcohol 12.2%, NSAID 7.1%; urticaria 100%, loss of consciousness 82.7%, dyspnoea 50.8%, hypotension 47.2%; 124/155 (80%) anaphylaxis-free after diagnosis; wheat-free diet effective in 91.7%, wheat– exercise avoidance 87%, reduced wheat + exercise avoidance 80.5%
42	Morita et al. (2022)	Japan	Prospective interventional physiological study	Healthy subjects, repeated challenge	Serum gliadin at 120 min 372 ± 233 pg/mL (first test) and $475 \pm$ 340 pg/mL (repeat), demonstrating within- subject reproducibility; cofactor-induced absorption attributed to prostaglandin-

					dependent tight-junction disruption independent of mast-cell activation
43	Chiang et al. (2023)	Hong Kong SAR	Prospective protocol-driven cohort (2017–2022)	161 referred patients; 131 met anaphylaxis criteria	Majority of anaphylaxis attributable to FDEIA, especially WDEIA; median diagnostic delay 2 y (range 0–30); paired tryptase obtained in only ~1/3, of which 82.5% significantly elevated; adrenaline auto-injector under-prescribed; FDEIA associated with later onset and more cardiovascular manifestations; SPT + sIgE diagnosed 95% of FDEIA
44	Chinuki et al. (2023)	Japan	Phase 2 multicentre single-arm interventional trial (UMIN000019250)	20 adults with WDEIA; 150–600 mg omalizumab	>80% achieved basophil activation <10% to all fractionated wheat

				s.c., 0–48 weeks, observation to 68 weeks	preparations; 68.8% of responders had no allergic reaction on wheat ingestion; after cessation, activation and reactions returned (up to 46.7% positive); no severe adverse events; desensitization not achieved
45	Aoki et al. (2023)	Japan	Case-control proteomic/diagnostic study	42 WDEIA (37 ω -5 gliadin sIgE-positive, 5 negative), 8 immediate wheat allergy, 20 healthy	Nine wheat proteins reactive in $\geq 60\%$ of patients; α/β gliadin MM1 positive in 23/26 (88%) ω -5-positive and 5/5 (100%) ω -5-negative patients; significantly higher basophil activation than non-allergic subjects
46	Dölle-Bierke et al. (2023)	Multinational (Europe)	Registry-based cross-sectional analysis	3,427 confirmed food-induced anaphylaxis cases	Age-dependent elicitor ranking (adults: wheat flour, shellfish, hazelnut, soy); exercise strongly

					associated with wheat anaphylaxis (Cramer's $V = 0.56$); wheat anaphylaxis cardiovascular in 75.7%; alcohol increased severity of wheat anaphylaxis (OR 3.23, 95% CI 1.31–8.83); exercise increased severity of peanut anaphylaxis (OR 1.78, 95% CI 1.09–2.95)
47	Scala et al. (2024)	Italy	Cross-sectional molecular study	1,203 food-allergic patients (ALEX-2 macroarray)	116 (9.6%) had food-dependent exercise-induced allergic reactions; among these 77 (66.3%) were LTP reactors and 16 (13.8%) Tri a 19-sensitized; LTPs and ω -5 gliadin were the only allergens clearly associated with FDEIAR; severity paralleled LTP sIgE

					level; FDEIAR patients had lower sIgE than food-allergic patients reacting at rest
48	Rymarczyk et al. (2025)	Poland	Single-centre prospective observational study with 1-year follow-up	28 adults with ≥ 1 anaphylactic episode	Mean age 39 ± 14.6 y; sIgE to highly allergenic components in 14; multi-family sensitization in 6 (21%); FDEIA subgroup of 4 tolerating all foods at rest; female sex identified as predisposing; no recurrence and no auto-injector use during 1-year follow-up after correct diagnosis and dietary education
49	Mukai et al. (2026)	Japan	Retrospective cohort (2012–2023) with 1-year follow-up	109 children aged 5–18 y undergoing exercise provocation	Of 53 with negative/indeterminate exercise provocation tests, 14 (26.4%) developed allergic

				testing after wheat oral immunotherap y	symptoms during follow-up (false negatives); higher ω -5 gliadin sIgE at testing significantly associated with events; all events occurred outdoors; age, sex, severity and exercise intensity not associated
50	Sridhara et al. (2026)	USA	Retrospective cohort/chart review (2017–2024)	7 adults aged 21–46 y (6 M, 1 F)	All had multiple Brown grade III anaphylactic episodes; predominant cardiovascular symptoms with minimal respiratory involvement; severity independent of exercise intensity and cofactor type; no correlation of ω -5 gliadin, wheat or gluten sIgE with severity; gluten-free diet prevented both

					anaphylaxis and intermittent urticaria, whereas cofactor separation prevented anaphylaxis only
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Table 8. Distribution of included studies by design, region and decade

Stratum	Category	n	% of 50
Design	Phase 2 interventional trial	1	2.0
	Prospective interventional / provocation study	14	28.0
	Retrospective cohort / clinical audit	11	22.0
	Case-control / diagnostic-accuracy study	9	18.0
	Cross-sectional / epidemiological survey	11	22.0
	Prospective observational cohort	4	8.0
Region	East Asia (Japan, China, Korea, Hong Kong)	22	44.0
	Western/Northern Europe (Denmark, Germany, UK, Finland, Poland)	10	20.0
	Mediterranean Europe (Italy, Spain, Portugal)	6	12.0
	North America / Oceania	4	8.0
	South-East Asia	1	2.0
	Multinational / mixed	7	14.0

Outcome Analyses

Prevalence and incidence

Five population-based surveys, all conducted in Japanese school populations and cumulatively enumerating more than 600,000 children, provide the only true population denominators available for this disorder. The earliest, surveying 11,647 children across three educational strata, found no cases in kindergarten, an incidence of 0.06% in elementary schools and 0.21% in junior high schools, the higher figure reflecting a case definition that admitted severe exertional urticaria. Applying a stricter anaphylaxis-based definition, a survey of 76,229 junior-

high-school students identified 13 FDEIA cases (0.017%) and 24 EIA cases (0.031%), and a subsequent multi-level survey of 353,977 students found FDEIA in 0.0085% and EIA in 0.012%. A later survey of 170,146 elementary schoolchildren identified only 8 cases (0.0047%), significantly fewer than the contemporaneous junior-high figure of 0.018% ($p = 0.0009$), establishing a robust and reproducible age gradient with pubertal amplification. Referral-based data corroborate the clinical weight of the disorder: in a protocol-driven Hong Kong anaphylaxis pathway, FDEIA — and specifically WDEIA — accounted for the majority of the 131 confirmed anaphylaxis cases, and in the European Anaphylaxis Registry exercise was the single most strongly associated cofactor for wheat-induced anaphylaxis (Cramer's $V = 0.56$).^{3,8,9,33,43,46}

Table 9. Population prevalence of FDEIA and EIA

Study	Population	Denominator	FDEIA cases	FDEIA prevalence	EIA cases	EIA prevalence	Notes
Tanaka (1994)	Kindergarten	11,647 (total)	0	0%	—	—	Definition included severe urticaria
Tanaka (1994)	Elementary school	(subset)	—	0.06%	—	—	31.1% of teachers aware
Tanaka (1994)	Junior high school	(subset)	—	0.21%	—	—	Highest reported figure
Aihara (2001)	Junior high school	76,229	13 (11 M, 2 F)	0.017%	24 (12 M, 12 F)	0.031%	Male excess for FDEIA ($p < .05$)
Aihara	Elementary	353,977	30 (24	0.0085%	44	0.012%	607 school

(2004)	+ junior + senior high		M, 6 F)		(22 M, 22 F)		nurses surveyed
Manabe (2018)	Elementary school	170,146	8	0.0047%	—	—	vs 0.018% junior high (p=0.0009); 4 additional post-OIT DEIA cases
Manabe (2015)	Junior high school (14- year comparison)	Yokohama cohort	—	Comparable to 2001	—	—	Awareness and preventive measures still limited

GRADE certainty: Low (observational survey designs; risk of ascertainment and reporting bias; single-country evidence base).

Demographic distribution and age of onset

Sex distribution is bidirectional and age-dependent. In school-based surveys FDEIA displayed a significant male excess (11 boys vs 2 girls; 24 males vs 6 females), whereas food-independent EIA showed no sex difference. In adult referral cohorts the pattern inverts or equalizes: a 10-year North American follow-up of 279 EIA patients comprised 199 women and 80 men with a mean age of 37.5 years and mean symptom duration of 10.6 years; a Chinese WDEIA cohort of 197 patients had a median age of 37 years and was 53.8% male; and a Polish prospective series identified female sex as a predisposing factor for exercise-induced food anaphylaxis. Age at first episode clusters in the second and third decades — most Japanese cases presented between 10 and 20 years, approximately half of 167 nationally reported cases were teenagers, and the mean age of onset in a Thai adult-onset wheat allergy cohort was 29.7 years. Paediatric FDEIA is concentrated

in adolescence, with a Korean series of 13 children all aged 13–17 years and predominantly male.^{6,7,8,9,32,39,41,48}

Table 10. Demographic characteristics across cohorts

Study	n	Setting	Male (%)	Age (median/mean)	Age at onset	Symptom duration before diagnosis
Shadick (1999)	279	Community EIA survey, USA	28.7	37.5 y (mean)	—	10.6 y (mean)
Harada (2000)	167	National case analysis, Japan	Male predominant	—	~50% teenagers	—
Aihara (2001)	13	School survey, Japan	84.6	12–15 y	12–15 y	—
Aihara (2004)	30	School survey, Japan	80.0	—	10–20 y	—
Song (2017)	13	Paediatric centre, Korea	76.9	13–17 y	13–17 y	1–7 episodes pre-diagnosis
Kennard (2018)	132	Multicentre adult, UK	—	Adult	—	>1 y in 69%
Thongngarm (2020)	33	Adult allergy clinic, Thailand	—	—	29.7 y (mean, SD 10.5)	—
Du (2022)	197	Tertiary centre, China	53.8	37 y (median)	—	16 months (median)
Chiang	131	Multidisciplinary	—	FDEIA later	Later than	2 y

(2023)		pathway, HK		onset	other anaphylaxis	(median, range 0– 30)
Sridhara (2026)	7	Tertiary centre, USA	85.7	21–46 y	—	Multiple grade III episodes

GRADE certainty: Low.

Culprit food spectrum and responsible molecules

Wheat is the dominant global culprit. In a systematic analysis of 167 Japanese cases, wheat accounted for more than half, followed by shrimp, with shrimp exceeding wheat in patients under 20 years. Wheat was the causative food in 4 of 8 Japanese elementary schoolchildren, in 46% of a Korean paediatric series, and constituted the leading adult elicitor of food-induced anaphylaxis in the European Anaphylaxis Registry. The earliest description implicated celery, and the earliest Japanese series implicated shellfish, wheat and grape, with four of eleven patients reacting to any food (non-specific FDEIA). The molecular picture is geographically bifurcated: in Mediterranean populations nsLTP predominates, with 78% of 82 Italian FDEIA patients sensitized to Pru p 3, and 66.3% of 116 patients with food-dependent exercise-induced allergic reactions in a 1,203-patient molecular cohort classified as LTP reactors compared with only 13.8% sensitized to Tri a 19. Critically, that study established LTPs and ω -5 gliadin as the *only* allergen families clearly associated with exercise-dependent reactions, and demonstrated that reaction severity tracked LTP-specific IgE titre. A minority of WDEIA is caused by wheat nsLTP (Tri a 14) rather than ω -5 gliadin, particularly in patients with concomitant severe peach allergy.^{1,2,7,19,24,32,33,46,47}

Table 11. Rank-ordered culprit foods and molecular archetypes

Study	Region	n	Leading culprit food(s)	Dominant molecule(s)	Proportion
Kidd (1983)	USA	4	Celery (3/4); any food (1/4)	Not characterized	75% celery

Dohi (1991)	Japan	11	Shellfish, wheat, grape; any food in 4	Not characterized	7/11 food-specific
Harada (2000)	Japan	167	Wheat > shrimp	Not characterized	Wheat >50%; shrimp first in <20 y
Romano (2012)	Italy	82	Tomato, cereals, peanut	Pru p 3 (nsLTP)	64/82 (78%) Pru p 3+
Pastorello (2014)	Italy	3	Wheat (with maize, rice)	Wheat 9-kDa nsLTP (Tri a 14)	3/3; ω-5 gliadin sIgE <0.35 kU/L in all
Song (2017)	Korea	13	Wheat 46%; rice, celery, cabbage, soybean, mungbean, fish	Not fully characterized	Wheat 46%
Manabe (2018)	Japan	8	Wheat 4/8; soy, fruit, crustacean, squid (1 each)	Not characterized	Wheat 50%
Dölle-Bierke (2023)	Europe	3,427	Adults: wheat flour, shellfish, hazelnut, soy	Wheat (exercise-associated)	Cramer's V 0.56 for exercise-wheat
Scala (2024)	Italy	116 FDEIAR of 1,203	Multiple plant foods	nsLTPs 66.3%; Tri a 19 13.8%	Only LTP and ω-5 gliadin associated with FDEIAR

GRADE certainty: Moderate (large, consistent, molecularly resolved cohorts; downgraded for indirectness of regional generalizability).

Triggering exercise modality and temporal windows

Aerobic, weight-bearing exertion predominates. In the largest EIA survey, jogging triggered attacks in 78% and brisk walking in 42% of 279 patients; ball games and running were the commonest triggers in Japanese schoolchildren. Reactions are, however, elicitable by exertion of strikingly low intensity — a brisk walk, occupational activity, dancing, and even the performance of cardiopulmonary resuscitation have been documented as sufficient. The temporal architecture is consistent across four decades: the maximal interval from food ingestion to symptom onset was 3.5 hours and from commencement of exercise to symptom onset 50 minutes in the earliest epidemiological survey, and the mean exercise-to-symptom interval was 21.6 minutes in a Korean paediatric cohort. Triangulating aggregative synthesis confirms that virtually all patients exercise within 4 hours of eating and develop symptoms within 1 hour of commencing exercise, with median intervals of 1 hour and 30 minutes respectively. These figures provide the empirical basis for the conventional 4-hour pre-exercise avoidance recommendation.^{3,4,6,9,24,32,53}

Table 12. Exercise modality and temporal windows

Parameter	Study	Finding
Jogging as trigger	Shadick (1999)	78% of 279 EIA patients
Brisk walking as trigger	Shadick (1999)	42%
Ball games and running	Aihara (2004)	Commonest in school populations
Low-intensity triggers documented	Pastorello (2014)	Brisk walk; workplace CPR; dancing
Maximal food→symptom interval	Tanaka (1994)	3.5 hours
Maximal exercise→symptom interval	Tanaka (1994)	50 minutes
Mean exercise→symptom interval (paediatric)	Song (2017)	21.6 minutes
Reactions during exercise (proportion of episodes)	Jiang (2018)	425/567 (75%)
Recommended pre-exercise avoidance	Romano (1995)	4 hours — abolished episodes in 12/14

interval		
Aggregative triangulation (median intervals)	Kulthanan (2022) [†]	Food→exercise 1 h; exercise→symptom 30 min

[†]Systematic review, retained for triangulation only per protocol.

GRADE certainty: Low.

Cofactor frequency and potency

Exercise is the most frequent but by no means the only augmenting factor. In 132 UK adults with ω-5 gliadin allergy the cofactor profile was exercise 80%, alcohol 25% and NSAID 9%, with 11% having no identifiable cofactor; in 197 Chinese WDEIA patients the profile was exercise 83.8%, alcohol 12.2% and NSAID 7.1%. Aspirin is a potent and independent augmenting factor: every Japanese patient subjected to aspirin provocation reacted, aspirin has been confirmed as an enhancing factor in children, and low-dose cardioprotective aspirin has been documented as sufficient. In LTP syndrome, 32.4% of anaphylactic episodes were cofactor-dependent. Registry data quantify the severity contribution of individual cofactors: alcohol raised the odds of severe wheat anaphylaxis more than threefold (OR 3.23, 95% CI 1.31–8.83) and exercise raised the odds of severe peanut anaphylaxis (OR 1.78, 95% CI 1.09–2.95).^{7,20,31,35,41,46}

Table 13. Frequency and effect of individual cofactors

Cofactor	Kennard (2018), n=132	Du (2022), n=197	Challenge positivity, Christensen (2019), n=25	Severity effect
Exercise	80%	83.8%	92%	Severity 0.8 → 2.1; OR 1.78 for severe peanut anaphylaxis (Dölle-Bierke 2023)
Aspirin / NSAID	9%	7.1%	84%	Severity 0.8 → 1.9; all aspirin-provoked cases

				reactive (Harada 2000)
Alcohol	25%	12.2%	56% (9/19)	Severity unchanged (0.8); OR 3.23 for severe wheat anaphylaxis (Dölle-Bierke 2023)
Exercise + aspirin	—	—	82%	Severity 1.5; greatest threshold reduction (87%)
No identifiable cofactor	11%	—	48% reacted at rest	Severity 0.8
Menstruation, infection, thermal extremes	Reported qualitatively	—	Not tested	Documented as modifiers (Sridhara 2026; Shadick 1999)

GRADE certainty: Moderate for exercise and aspirin (consistent dose–response across independent challenge cohorts); Low for alcohol and other cofactors (inconsistent, imprecise).

Clinical manifestations and severity

Cutaneous involvement is near-universal and cardiovascular involvement disproportionately frequent relative to other food anaphylaxis phenotypes. In the largest single-centre WDEIA cohort, urticaria occurred in 100%, loss of consciousness in 82.7%, dyspnoea in 50.8% and hypotension in 47.2%. In 283 Chinese WDEIA patients, 415 of 567 documented reactions (73.3%) were potentially life-threatening. Registry analysis found wheat-induced anaphylaxis to be cardiovascular in 75.7% of cases, the highest of any elicitor. A recent US cohort of seven patients found predominant cardiovascular symptoms with minimal respiratory involvement in all, and severity that was independent of exercise intensity and of the specific cofactor deployed — a pattern the authors interpreted as evidence of a mechanism distinct from classical food allergy. The HWP-sensitized subtype displays a divergent phenotype dominated by facial angioedema with significantly less frequent blood-pressure reduction.^{21,36,41,46,50}

Table 14. Organ-system involvement and severity

Manifestation	Du (2022), n=197	Jiang (2018), n=283 (567 reactions)	Dölle-Bierke (2023), wheat FIA	Sridhara (2026), n=7	Hiragun (2013), HWP subtype
Urticaria / wheals	100%	Predominant	Frequent	All (intermittent, wheat-related)	Frequent
Angioedema	Frequent	Frequent	Frequent	Frequent	Predominant (facial/eyelid)
Loss of consciousness	82.7%	Frequent	—	Present in all	Less frequent
Dyspnoea / respiratory	50.8%	Frequent	—	Minimal	Variable
Hypotension / cardiovascular	47.2%	73.3% life-threatening	75.7%	Predominant	Significantly less frequent than conventional WDEIA
Gastrointestinal	Reported	Reported	Reported	Reported	Reported
Severity grade	—	73.3% life-threatening	—	All Brown grade III	Generally milder haemodynamically

GRADE certainty: Moderate.

Diagnostic accuracy of component-resolved specific IgE

Component-resolved serology transformed the diagnosis of WDEIA. Whole-wheat and gluten sIgE perform poorly (sensitivity 48% and 56% respectively), whereas recombinant ω -5 gliadin achieved 80% sensitivity with the highest area under the receiver-operating-characteristic curve (0.850) in a three-group case-control design. Sensitivity rises further with molecular

combination: recombinant HMW-glutenin alone was highly specific (92.9%) but insensitive (16.7%), yet in combination with recombinant ω -5 gliadin achieved 93.8% sensitivity and 92.9% specificity. In a large Chinese diagnostic cohort with four comparator groups, gluten sIgE achieved the highest AUC (0.910) followed by ω -5 gliadin (0.879), and the combination yielded 73.1% sensitivity with 99.0% specificity — a profile favouring rule-in diagnosis without challenge. Challenge-anchored Danish data reported ω -5 gliadin sensitivity 91% and specificity 92%, best when gluten was combined with exercise, and an Australian audit reported identical figures. Approximately 80% of WDEIA patients react to ω -5 gliadin and the remainder principally to HMW-glutenin. Newer markers extend coverage of seronegative patients: α/β gliadin MM1 was positive in 88% of ω -5 gliadin-positive and 100% of ω -5 gliadin-negative WDEIA patients. Paediatric performance is inferior, and molecular panels are required in children.^{11,12,13,18,30,34,36,39,45}

Table 15. Diagnostic accuracy of component-resolved specific IgE

Index test	Study	Reference standard	Sensitivity	Specificity	AUC	Comparator groups
Wheat sIgE	Matsuo (2008)	Clinical + challenge	48%	—	—	25 healthy, 25 AD
Gluten sIgE	Matsuo (2008)	Clinical + challenge	56%	—	—	as above
Gluten sIgE	Jiang (2018)	Expert clinical evaluation	—	—	0.910	133 non-wheat anaphylaxis, 186 urticaria, 94 healthy
ω -5 gliadin epitope peptide (Pep A)	Matsuo (2008)	Clinical + challenge	76%	—	—	as above
HMW-glutenin epitope peptide	Matsuo (2008)	Clinical + challenge	22%	—	—	as above

(Pep B)						
Recombinant ω-5 gliadin	Matsuo (2008)	Clinical + challenge	80%	—	0.850	as above
Recombinant ω-5 gliadin	Christensen (2018)	Titrated gluten + exercise challenge	91%	92%	—	Challenge- negative patients
ω-5 gliadin sIgE	Le (2016)	Clinical wheat- related symptoms	91%	92%	—	sIgE-negative comparison group
ω-5 gliadin sIgE	Jiang (2018)	Expert clinical evaluation	—	—	0.879	as above
Recombinant HMW-glutenin	Takahashi (2012)	Clinical WDEIA	16.7%	92.9%	—	16 AD, 12 healthy
rω-5 gliadin + rHMW- glutenin combined	Takahashi (2012)	Clinical WDEIA	93.8%	92.9%	—	as above
Gluten + ω-5 gliadin combined	Jiang (2018)	Expert clinical evaluation	73.1%	99.0%	—	as above
Epitope peptides (ω-5 gliadin + HMW-	Matsuo (2005b)	Clinical WDEIA	29/30 (96.7%)	25/25 healthy negative	—	25 healthy, 25 AD

glutenin)							
ω-5 gliadin sIgE (adult-onset wheat allergy)	Thongngarm (2020)	3-day cofactor challenge	88% positivity	—	—	Within-cohort	
α/β gliadin MM1	Aoki (2023)	Clinical WDEIA	88% of ω-5+; 100% of ω-5−	—	—	8 wheat allergy, 20 healthy	
SPT wheat / gluten	Christensen (2018)	Titrated challenge	93.6% / 95.7%	—	—	Within-cohort	

GRADE certainty: Moderate (consistent, reproducible estimates across four independent countries; downgraded for reference-standard heterogeneity and absence of consecutive-sampling in several case-control designs).

Skin and cellular test performance

Skin testing performance depends critically on the antigen preparation. Commercial wheat extracts perform poorly (9.1% positivity in a Thai cohort), whereas in-house gliadin and glutenin extracts achieved 84.8% and 81.8% positivity in the same patients, and gluten skin prick testing achieved challenge-confirmed sensitivity of 100% with specificity 96%. Skin prick testing to wheat and gluten was positive in 93.6% and 95.7% of challenge-confirmed Danish patients, and ω-5 gliadin skin prick testing achieved 92% sensitivity and 84% specificity in an Australian audit. Prick-plus-prick testing with fresh foods and broad-panel testing disclosed hypersensitivities missed by commercial extracts, and each test modality identified positivities not detected by the others — supporting a multimodal rather than sequential diagnostic strategy. Basophil activation testing using CD203c expression discriminated HWP-sensitized from conventional WDEIA with complete concordance, and basophil activation has been used as the primary efficacy endpoint in interventional trials.^{4,17,19,25,30,34,39,44}

Table 16. Performance of skin and cellular tests

Test	Study	Sensitivity / positivity	Specificity	Comment
SPT commercial wheat extract	Thongngarm (2020)	9.1%	—	Inadequate as sole test
SPT in-house gliadin	Thongngarm (2020)	84.8%	—	Marked superiority of native preparation
SPT in-house glutenin	Thongngarm (2020)	81.8%	—	—
SPT gluten	Brockow (2015)	100%	96%	Challenge-confirmed
SPT wheat	Christensen (2018)	93.6%	—	Challenge-confirmed
SPT gluten	Christensen (2018)	95.7%	—	Challenge-confirmed
SPT ω -5 gliadin	Le (2016)	92%	84%	Comparable to sIgE
Prick + prick fresh foods	Romano (1995, 2012)	Complementary	—	Detected positivities missed by extracts and CAP
BAT (CD203c)	Chinuki (2012)	Complete subtype discrimination	—	HWP-A vs purified ω -5 gliadin
BAT (fractionated wheat)	Chinuki (2023)	Used as primary trial endpoint	—	<10% activation achieved in >80% on omalizumab
BAT (α/β gliadin MM1)	Aoki (2023)	Significantly higher than controls	—	14 WDEIA vs 5 non-allergic
SPT + sIgE combined	Chiang (2023)	95% of FDEIA diagnosed	—	Avoids challenge in most patients

GRADE certainty: Moderate.

Provocation challenge diagnostic yield

Challenge testing remains the reference standard but is protocol-dependent and imperfectly sensitive. A German gluten-based protocol confirmed WDEIA in 16 of 16 challenged patients — four with gluten alone and twelve with gluten plus cofactors — including four patients with previously negative conventional wheat challenges, and concluded that exercise is not an essential trigger. A Danish protocol elicited reactions in 47 of 71 patients (66%). A Thai modified three-day protocol combining 300 mg acetylsalicylic acid, 60–75 g wheat flour and exercise achieved 94.4% positivity (17/18), at the cost of one hypotensive anaphylaxis. Serum gliadin monitoring during challenge reclassified challenge-negative patients into definite, probable and non-WDEIA categories, materially reducing false-negative misclassification. In children desensitized by wheat oral immunotherapy, 26.4% of those with negative or indeterminate exercise provocation tests nevertheless developed field reactions within one year, with higher ω -5 gliadin sIgE the only associated predictor.^{8,23,25,32,34,39,49}

Table 17. Diagnostic yield of provocation challenge protocols

Study	Protocol	n challenged	Positive	Yield	False-negative burden	Adverse events
Aihara (2001)	Food + exercise, school setting	5 of 13	5	100 % of those tested	—	None reported
Brockow (2015)	Titrated gluten $\pm$ ASA/alcohol/exercise	16	16	100 %	4 previously wheat-challenge	Not specified

					-negative captured	
Kohno (2013)	Wheat + exercise and/or aspirin, with serum gliadin monitoring	36	17	47%	Gliadin monitorin g reclassifie d 9 of 19 negatives	—
Song (2017)	Food + exercise, paediatric	8	7	87.5 %	—	3/7 severe, IV adrenaline
Christense n (2018)	Titrated gluten at rest then with treadmill	71	47	66%	24 non- reactors	Not specified
Christense n (2019)	Titrated gluten with 5 cofactor arms	25	23 (with exercis e)	92%	—	Not specified
Thongngar m (2020)	3-day: ASA 300 mg + 60–75 g wheat flour + exercise	18	17	94.4 %	—	1 hypotensi ve anaphylax is
Mukai (2026)	Exercise provocation after wheat OIT	109 (53 negative/indetermina te)	—	—	14/53 (26.4%) field reactions	Field reactions all outdoors

					within 1 year	
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GRADE certainty: Moderate.

Cofactor effect on eliciting threshold and severity

This domain provides the strongest and most internally consistent quantitative evidence in the review. In 71 patients challenged with titrated gluten, the median eliciting dose was 48 g at rest and 24 g with treadmill exercise, and mean Sampson severity rose from 1.1 to 2.3. A dedicated multi-cofactor titration in 25 patients established a rank-ordered hierarchy: median eliciting dose 8 g with aspirin, 24 g with exercise, 28 g with alcohol, and 4.3 g with exercise plus aspirin, corresponding to threshold reductions of 83%, 63%, 36% and 87% respectively relative to rest. Mean severity rose from 0.8 at rest to 2.1 with exercise and 1.9 with aspirin, but was unchanged by alcohol. Plasma gliadin threshold levels associated with positive challenge varied more than one hundredfold across individuals (15–2,111 pg/mL, median 628), establishing marked inter-individual variation in the permeability–reactivity relationship.^{25,34,37}

Table 18. Eliciting threshold and severity by cofactor (Christensen 2019, n = 25; Christensen 2018, n = 71)

Condition	Challenge positivity	Median eliciting gluten dose	Range	Threshold reduction vs rest	Mean Sampson severity (0–5)
Rest (no cofactor)	48% (12/25); 37% of reactors in the 71-patient cohort	48 g	8–80 g	Reference	0.8 (1.1 in n=71 cohort)
Exercise	92% (23/25)	24 g	4.8–80 g	–63%	2.1 (2.3 in n=71 cohort)
Aspirin	84% (21/25)	8 g	2.4–80 g	–83%	1.9
Alcohol	56% (9/19)	28 g	0–45 g	–36%	0.8

Exercise + aspirin	82% (18/22)	4.3 g	1.1–48 g	–87%	1.5
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GRADE certainty: Moderate (two independent prospective titration cohorts with concordant direction and magnitude; downgraded for imprecision and absence of blinding/randomization).

Mechanistic biomarkers

Immunoreactive gliadin appears in serum during wheat-plus-exercise and wheat-plus-aspirin challenge in parallel with clinical symptoms, and — decisively for mechanism — the same rise occurs in non-sensitized healthy volunteers who develop no symptoms, whereas wheat alone produces only low serum gliadin. Non-steroidal anti-inflammatory drugs increase post-ingestion serum allergen levels in a manner dependent on cyclooxygenase inhibition profile. The within-subject reproducibility of the gliadin rise has been confirmed (372 ± 233 pg/mL versus 475 ± 340 pg/mL on repeat testing) and attributed to impaired enterocyte tight-junction sealing consequent on prostaglandin inhibition, a mechanism supported by the demonstration that premedication with a synthetic prostaglandin E1 analogue abolishes both the gliadin rise and the clinical reaction provoked by aspirin. A dissenting prospective crossover in 12 healthy volunteers found that cofactors did *not* substantially raise peak gliadin concentrations, although they markedly increased inter-individual variability, and that stool zonulin was unrelated to cofactor exposure or peak gliadin — leading those authors to propose that WDEIA patients possess a specific predisposition (hyperresponsive or damaged intestinal epithelium) and that alternative mechanisms including blood-flow redistribution, tissue transglutaminase activation and plasma hyperosmolality may predominate. Mediator studies demonstrate transient plasma histamine elevation after exercise challenge without corresponding tryptase rise in school-age patients, whereas paired acute tryptase sampling in an emergency-referral cohort was significantly elevated in 82.5% of the minority in whom it was obtained.^{2,9,10,14,15,23,25,38,42,43}

Table 19. Mechanistic biomarker findings

Biomarker	Study	Principal finding	Interpretation
Serum	Matsuo	Rises with wheat+exercise and	Cofactor-driven permeability

immunoreactive gliadin	(2005a)	wheat+aspirin in patients <i>and</i> healthy controls; low with wheat alone	is not disease-specific
Serum gliadin (NSAID class effect)	Matsuo (2009)	Low-dose aspirin, diclofenac, loxoprofen, meloxicam differentially raise serum gliadin	COX-inhibition-dependent absorption
Serum gliadin (reproducibility)	Morita (2022)	$372 \pm 233 \rightarrow 475 \pm 340$ pg/mL on repeat	Reproducible within-subject; wide between-subject variation
Serum gliadin (threshold)	Brockow (2015)	Positive threshold 15–2,111 pg/mL (median 628); >100-fold variation	Individual reactivity set-point
Serum gliadin (diagnostic use)	Kohno (2013)	Monitoring reclassified challenge-negative patients	Adjunct to reduce false negatives
Serum gliadin (cofactor effect in health)	Scherf (2019)	Cofactors did not substantially raise peak levels; variability increased ($p < 0.001$)	Challenges the simple permeability model
Stool zonulin	Scherf (2019)	Unrelated to cofactor or peak gliadin; microbiota differed by zonulin stratum	Zonulin not a useful surrogate
Prostaglandin E1 analogue	Inoue (2009)	Misoprostol premedication suppressed gliadin rise and urticaria	Prostaglandin-dependent tight-junction mechanism
Plasma histamine	Dohi (1991)	Rose after treadmill challenge in 6/11	Mast-cell/basophil degranulation
Plasma histamine /	Aihara	Transient histamine rise	Compartmentalized mediator

tryptase	(2004)	without tryptase elevation	release
Serum tryptase (acute, paired)	Chiang (2023)	Obtained in ~1/3 of cases; 82.5% of those significantly elevated	Under-utilized confirmatory test
Basophil CD203c	Chinuki (2012)	Subtype-discriminating; abolished by surface-IgE removal	IgE-mediated, allergen- specific
Tissue transglutaminase cross-linking	Palosuo (2003) [†]	tTG cross-linking increased IgE binding; SPT wheal 77% larger than untreated peptic fraction	Exercise-induced tTG activation may generate high-avidity complexes

[†]Retained for mechanistic triangulation.

GRADE certainty: Low to Moderate (mechanistically informative but with one directly contradictory prospective study).

Treatment, prophylaxis and effectiveness

Avoidance is highly but incompletely effective, and the two competing avoidance strategies are not equivalent. In 155 followed Chinese patients, a wheat-free diet prevented further anaphylaxis in 91.7%, avoidance of wheat in combination with exercise in 87.0%, and reduced wheat intake with exercise avoidance in 80.5%; overall 124/155 (80%) had no further anaphylaxis. In 132 UK adults, gluten-free diet reduced subsequent reactions by 67% and wheat–exercise avoidance by 69%, but one third continued to react despite dietary advice. A recent cohort clarified the qualitative difference: a gluten-free diet prevented both anaphylaxis and the intermittent urticaria that accompanied ordinary wheat ingestion, whereas separating gluten from cofactors prevented anaphylaxis only. Four-hour pre-exercise food avoidance abolished further episodes in 12 of 14 Italian patients, and adherent Finnish patients on a gluten-free or wheat-free diet remained symptom-free except when wheat was inadvertently consumed. Pharmacological options are limited: misoprostol premedication suppressed aspirin-provoked reactions in a provocation setting, and a phase 2 single-arm trial of omalizumab in 20 adults achieved basophil activation below 10%

in more than 80% of patients, with 68.8% of these experiencing no allergic reaction on wheat ingestion — but the effect waned after cessation, with up to 46.7% again reacting, and desensitization was not achieved. Universal adrenaline auto-injector provision is therefore mandatory irrespective of dietary strategy.^{4,5,15,35,36,41,44,50}

Table 20. Effectiveness of management strategies

Strategy	Study	n	Effectiveness	Residual risk
Wheat-free diet	Du (2022)	155 followed	91.7% anaphylaxis-free	8.3% continued to react
Avoidance of wheat combined with exercise	Du (2022)	155 followed	87.0%	13.0%
Reduced wheat + exercise avoidance	Du (2022)	155 followed	80.5%	19.5%
Overall post-diagnosis outcome	Du (2022)	155	124 (80%) anaphylaxis-free	20% recurrent
Gluten-free diet	Kennard (2018)	132	67% reduction in reactions	~33% continued to react
Wheat–exercise avoidance	Kennard (2018)	132	69% reduction	~31%
Gluten-free diet vs cofactor separation	Sridhara (2026)	7	GFD prevented anaphylaxis and intermittent urticaria; separation prevented anaphylaxis only	Urticaria persisted with separation strategy
4-hour pre-	Romano	14	Episodes abolished in	2 required elimination

exercise food avoidance	(1995)		12	of all pre-exercise meals
Gluten-free / wheat-free diet	Palosuo (1999)	18	Adherent patients symptom-free	3 reacted after inadvertent wheat ingestion
Strict avoidance + patient education	Jiang (2018)	283, 1-year follow-up	Repeat anaphylaxis rare	Not quantified
Diagnosis + dietary education	Rymarczyk (2025)	28	No recurrence, no auto-injector use at 1 year	Small sample
Misoprostol (PGE1 analogue) premedication	Inoue (2009)	2 (provocation)	Suppressed gliadin rise and urticaria	Proof-of-concept only
Omalizumab 150–600 mg s.c., 48 weeks	Chinuki (2023)	20	>80% achieved BAT <10%; 68.8% of responders reaction-free; no severe adverse events	Effect waned after cessation (up to 46.7% reactive); desensitization not achieved

GRADE certainty: Low (avoidance strategies — observational, unblinded, adherence-confounded); Moderate for omalizumab biomarker endpoint but Low for clinical endpoint (single-arm, uncontrolled, n = 20).

Recurrence, natural history and remission

The natural history of exercise-induced allergy is one of gradual attenuation without reliable resolution. In a 10-year follow-up of 279 EIA patients, attack frequency had decreased in 47% and stabilized in 46%, and 41% reported being completely attack-free during the preceding year; improvement was attributed to individual modification of exercise habits and avoidance of

environmental and ingestible precipitants (avoidance of extreme temperatures 44%, pre-exercise foods 37%, allergy-season exercise 36%, humid weather 33%). Against this, approximately 20% of a large diagnosed WDEIA cohort continued to experience anaphylaxis after diagnosis, and one third of a UK ω -5 gliadin cohort continued to react despite dietary counselling. The HWP-sensitized subtype is prognostically distinct: sensitivity to gluten and glutenins declined over months following soap discontinuation, and formal Kaplan–Meier analysis of 110 patients quantified clinical remission and negative conversion of ex vivo histamine release after cessation of the causative product — the only documented pathway to genuine remission in this disorder. In post-oral-immunotherapy patients, 26.4% with negative exercise provocation tests reacted within one year, indicating that a negative provocation test does not confer durable safety.^{6,21,29,35,41,49}

Table 21. Recurrence, remission and natural-history trajectory

Study	Population	Follow-up	Trajectory	Key figure
Shadick (1999)	279 EIA	10 years	Attenuating	47% decreased, 46% stabilized, 41% attack-free in past year
Hiragun (2013)	36 WDEIA (30 HWP)	Months	Improving after exposure cessation	Gluten/glutenin sensitivity declined
Hiragun (2016)	110 HWP-wheat allergy	To 2014	Remission achievable	Kaplan–Meier remission and HRT negative-conversion rates
Kobayashi (2015)	61 soap users	Clinical course	Heterogeneous	Six clinical phenotype groups
Kennard (2018)	132	Post-diagnosis	Incomplete control	~33% continued to react
Du (2022)	155 followed	Post-diagnosis	Largely controlled	80% anaphylaxis-free; ~20% recurrent
Jiang (2018)	283	1 year	Controlled with	Repeat anaphylaxis rare

			avoidance	
Mukai (2026)	53 provocation- negative children	1 year	Unreliable reassurance	26.4% developed field reactions
Rymarczyk (2025)	28	1 year	Controlled	No recurrence

GRADE certainty: Low.

Diagnostic delay, misdiagnosis and quality-of-care indicators

Diagnostic delay is the single most consistent care-quality deficiency identified. In 132 UK adults, 40% experienced a delay of 1–5 years and a further 29% a delay exceeding 5 years. In 197 Chinese patients the median duration of anaphylaxis before diagnosis was 16 months, with delay exceeding one year in 52.7% and — critically — no improvement across calendar time ($p = 0.064$). In a Hong Kong multidisciplinary pathway the median delay was 2 years with a range extending to 30 years. Contributory factors are institutional as well as clinical: only one third of Japanese junior-high-school nurses had any knowledge of FDEIA, and only 31.1% of teachers in an earlier survey; seventeen of 167 nationally reported Japanese episodes occurred during the school lunch recess or physical-education class. Acute-care performance is likewise deficient: paired serum tryptase was obtained in only about one third of anaphylaxis presentations, and adrenaline auto-injectors were systematically under-prescribed, particularly for food-related anaphylaxis. Because ω -5 gliadin allergy frequently presents as apparently idiopathic anaphylaxis — 10 of 67 patients in one audit — routine ω -5 gliadin sIgE testing has been recommended for all adults presenting with anaphylaxis of unclear cause.^{3,7,8,30,35,41,43}

Table 22. Diagnostic delay and care-quality indicators

Indicator	Study	Finding
Delay 1–5 years	Kennard (2018)	40% of 132 adults
Delay >5 years	Kennard (2018)	29% of 132 adults

Median delay	Du (2022)	16 months; >1 year in 52.7%; no temporal improvement (p=0.064)
Median delay	Chiang (2023)	2 years (range 0–30)
Presentation as idiopathic anaphylaxis	Le (2016)	10/67 ω -5 gliadin-positive patients
School-nurse awareness	Aihara (2001)	Only one third aware of FDEIA
Teacher awareness	Tanaka (1994)	31.1% had heard of the condition
Episodes occurring at school	Harada (2000)	17/167 during lunch recess or PE class
Paired acute tryptase obtained	Chiang (2023)	~1/3 of anaphylaxis cases; 82.5% of those elevated
Adrenaline auto-injector prescription	Chiang (2023)	Under-prescribed, especially in food-related anaphylaxis

GRADE certainty: Moderate.

Hydrolysed-wheat-protein subtype and post-immunotherapy phenotype

The hydrolysed-wheat-protein epidemic constitutes an unintended human sensitization experiment of exceptional evidential value. Five Japanese women developed WDEIA one to three years after commencing use of a single hydrolysed-wheat-protein facial soap, with IgE reactivity significantly higher to HWP than to natural wheat protein and inhibition studies demonstrating unidirectional inhibition — confirming HWP as the primary sensitizer. In a subsequent cohort of 36 WDEIA patients, 30 had used only that soap; these patients were predominantly female, presented with facial symptoms and angioedema, had less frequent blood-pressure reduction, and had gluten-specific IgE exceeding ω -5 gliadin-specific IgE. Immunochemical characterization of 22 such patients localized IgE binding to α/β -, γ - and ω 1,2-gliadins, with recombinant γ -gliadin inducing

histamine release in 8 of 11 and an epitope (QPQQPFPQ) identified whose deamidated form bound IgE more strongly than the native sequence. Basophil CD203c testing discriminated the two subtypes completely. Angiotensin-converting-enzyme genotype was implicated as a host risk modifier in 47 affected patients. In 61 soap users, 35 developed food reactions, 18 were skin-test positive to 0.01% Glupearl 19S, and six clinical phenotypes were delineated. Separately, oral immunotherapy has generated a novel phenotype — desensitization-status exercise-induced anaphylaxis — identified in four Japanese elementary schoolchildren and characterized in 109 children undergoing exercise provocation after wheat oral immunotherapy, of whom 26.4% with negative tests subsequently reacted in the field.^{16,17,21,22,26,27,29,33,49}

Table 23. Conventional versus HWP-sensitized WDEIA and post-OIT phenotype

Feature	Conventional WDEIA	HWP-sensitized WDEIA	Post-OIT exercise-induced allergic reaction
Route of primary sensitization	Gastrointestinal	Percutaneous / rhinoconjunctival (facial soap)	Induced oral desensitization
Sex distribution	Male-predominant in adolescence	Predominantly female	Paediatric, both sexes
Dominant allergen	ω -5 gliadin; HMW-glutenin	α/β -, γ -, ω 1,2-gliadins; γ -gliadin epitope QPQQPFPQ	ω -5 gliadin (higher sIgE predicts events)
ω -5 gliadin sIgE	Positive in ~80%	Low or absent	Positive
Gluten sIgE relative to ω -5 gliadin	Lower	Higher ($p < 0.05$)	—
Predominant clinical features	Urticaria, hypotension, collapse	Facial/eyelid angioedema; contact urticaria; less hypotension	Exercise-induced reactions after previously tolerated

			dose
Basophil CD203c response	To purified ω-5 gliadin only	To HWP-A only	Not characterized
Host risk modifier	—	ACE insertion/deletion genotype	Higher ω-5 gliadin sIgE
Prognosis	Chronic; attenuating	Remission achievable after exposure cessation	26.4% field reactions despite negative provocation
Key studies	Matsuo 2005/2008; Morita 2009; Christensen 2018	Fukutomi 2011; Hiragun 2013/2016; Yokooji 2013; Kobayashi 2015; Sugiyama 2015; Chinuki 2012	Manabe 2018; Mukai 2026

GRADE certainty: Moderate for phenotypic distinction; Low for host genetic association and for post-OIT prognosis.

Certainty of Evidence

Table 24. GRADE summary of findings across outcome domains

Domain	Body of eviden ce	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisi on	Publicati on bias	Certain ty
O1 Prevalence	5 surveys	Serio us	Not serious	Serious (single country)	Not serious	Suspected	Low
O2 Demographics	10 cohorts	Serio us	Serious	Not serious	Not serious	Undetecte d	Low
O3 Culprit	9	Not	Not serious	Serious	Not	Undetecte	Moderate

foods	studies	serious		(regional)	serious	d	te
O4 Exercise & timing	6 studies	Serious	Not serious	Not serious	Serious	Undetected	Low
O5 Cofactors	6 studies	Not serious	Not serious	Not serious	Serious	Undetected	Moderate
O6 Manifestations	5 cohorts	Not serious	Not serious	Not serious	Not serious	Undetected	Moderate
O7 Component sIgE accuracy	9 studies	Not serious	Not serious	Serious (reference standard)	Not serious	Undetected	Moderate
O8 Skin/cellular tests	8 studies	Serious	Not serious	Not serious	Not serious	Undetected	Moderate
O9 Challenge yield	8 studies	Not serious	Serious	Not serious	Not serious	Undetected	Moderate
O10 Threshold/severity	3 titration studies	Not serious	Not serious	Not serious	Serious	Undetected	Moderate
O11 Biomarkers	11 studies	Serious	Very serious (contradictory)	Not serious	Serious	Undetected	Low
O12 Treatment	8	Very	Not serious	Not	Serious	Suspected	Low

		studies	serious		serious			
O13	Natural history	9 studies	Serious	Serious	Not serious	Serious	Suspected	Low
O14	Care quality	7 studies	Not serious	Not serious	Not serious	Not serious	Undetected	Moderate
O15	HWP / post-OIT	9 studies	Serious	Not serious	Serious	Not serious	Undetected	Low–Moderate

DISCUSSION

Principal Findings

This systematic review of fifty analytical primary studies published across four decades establishes six principal findings. First, food-dependent exercise-induced anaphylaxis is a rare but not negligible disorder, with an age-stratified population prevalence rising from 0.0047% in elementary schoolchildren to 0.017–0.018% in junior-high-school students, and constituting the leading identifiable cause of anaphylaxis in at least one specialist referral pathway. Second, two molecular archetypes dominate globally — an ω -5 gliadin/HMW-glutenin archetype and a non-specific lipid transfer protein archetype — whose relative frequency is determined principally by geography and by route of primary sensitization. Third, exercise is a threshold-lowering and severity-amplifying cofactor rather than an obligatory elicitor, since reactions are reproducibly provoked at rest with sufficient allergen dose in 37–48% of patients. Fourth, cofactors exert quantifiable, rank-ordered and additive effects on eliciting threshold, with the combination of exercise and aspirin producing an 87% threshold reduction. Fifth, component-resolved serology, particularly in molecular combination, achieves diagnostic performance sufficient to obviate provocation challenge in the majority of adults. Sixth, structured avoidance is highly but

incompletely effective, leaving a residual breakthrough risk of approximately one in five to one in three patients that mandates universal adrenaline auto-injector provision.^{3,8,25,33,34,36,37,41,43,47}

Nosological Reconceptualization: A Continuum Rather Than a Dichotomy

The traditional taxonomy places EIA and FDEIA within “physical allergy”, implying that the physical stimulus is the antigenic or quasi-antigenic driver. The evidence synthesized here is incompatible with that framing. Titrated gluten challenge demonstrated a clinical reaction at rest in 26 of 47 reactors (37%), and a dedicated cofactor-titration study demonstrated positive challenge at rest in 48% of patients; German investigators confirmed WDEIA in 16 of 16 patients using gluten with or without cofactors and concluded explicitly that exercise is not an essential trigger. It follows that FDEIA is most accurately characterized as a **high-threshold, cofactor-dependent IgE-mediated food allergy** in which the habitual dietary dose lies beneath the resting eliciting threshold but above the cofactor-reduced threshold. Under this model, the apparent categorical distinction between food-dependent and food-independent EIA collapses into a continuum governed by three variables: the quantity and molecular form of allergen ingested, the aggregate cofactor load, and the individual’s epithelial permeability and mast-cell reactivity set-point. Cases labelled “food-independent EIA” plausibly represent the extreme of this continuum in which the culprit allergen has not been identified — a hypothesis supported by the observation that 16 of 67 patients with ω -5 gliadin sensitization presented with exercise-induced symptoms without any apparent food association, and that 10 presented as idiopathic anaphylaxis.^{25,30,34,37,60}

This reconceptualization has three practical corollaries. It explains why negative food–exercise challenges are common yet do not exclude the diagnosis; it justifies the use of high-dose gluten challenge and multiple cofactor arms rather than reliance on a single naturalistic reproduction attempt; and it predicts that the same patient may react on one occasion and not another with identical food and exercise, because unmeasured cofactors (ambient temperature, concurrent infection, menstrual phase, fasting state, alcohol, analgesics) fluctuate. The empirical observation that clinical reproducibility is low, and that up to 30% of double-blind placebo-controlled food-exercise challenges are negative in genuinely affected patients, follows directly.^{25,34,37,53,60}

The Two Molecular Archetypes and Their Geography

The gliadin archetype and the LTP archetype have developed as largely separate literatures, and their reconciliation is one of the principal contributions of this synthesis. In East Asia, Northern Europe, the United Kingdom and Australia, ω -5 gliadin (Tri a 19) is the dominant sensitizer, present in approximately 80–91% of WDEIA patients, with high-molecular-weight glutenin subunit accounting for most of the remainder. In Italy and Spain, non-specific lipid transfer proteins dominate: 78% of 82 Italian FDEIA patients were Pru p 3-sensitized, and in a 1,203-patient molecular cohort 66.3% of those with exercise-dependent reactions were LTP reactors compared with 13.8% sensitized to Tri a 19. Crucially, that study established that LTPs and ω -5 gliadin were the *only* allergen families clearly associated with exercise dependence, indicating that the capacity to produce a cofactor-dependent phenotype is a property of specific molecular families rather than a generic feature of food allergens.^{12,13,19,30,34,47}

The structural basis of this molecular selectivity is instructive. Both archetypes comprise proteins that are unusually resistant to gastric and intestinal proteolysis — nsLTPs by virtue of a compact four-disulphide-stabilized fold, and the prolamins by virtue of repetitive proline- and glutamine-rich sequences. Both therefore reach the intestinal epithelium in immunologically intact form, and both are candidates for cofactor-augmented paracellular transit. Omega-5 gliadin possesses the additional property of being a substrate for tissue transglutaminase, whose cross-linking of peptic fragments increases IgE binding in vitro and enlarges skin-test wheals by 77% in vivo — furnishing a specific molecular mechanism by which exercise, which upregulates interleukin-6-driven tissue transglutaminase expression, could convert a tolerated protein into a multivalent, high-avidity anaphylactogen. That the two archetypes are not mutually exclusive is demonstrated by patients in whom WDEIA is caused by wheat nsLTP (Tri a 14) with undetectable ω -5 gliadin sIgE, typically in the context of severe concomitant peach allergy, and by the emergence of LTP-associated FDEIA in East Asian populations previously considered gliadin-dominant.^{19,24,47,51,61}

The clinical implication is that the diagnostic algorithm must be geographically and phenotypically calibrated. In a patient of Northern European or East Asian background with wheat-

associated exertional anaphylaxis, ω -5 gliadin sIgE — supplemented by HMW-glutenin and, where available, α/β gliadin MM1 — is the appropriate first-line test. In a patient of Mediterranean background, or in any patient with multiple taxonomically unrelated plant-food reactions, pollinosis, or a history of severe peach allergy, an nsLTP-oriented panel anchored on Pru p 3 with extension to Tri a 14, Jug r 3, Ara h 9, Cor a 8 and Art v 3 is required. Applying the wrong panel produces a false-negative result and perpetuates the diagnosis of idiopathic anaphylaxis.^{19,24,40,45,47,61}

The Cofactor Hierarchy and Its Clinical Application

The convergence of two independent Danish titration cohorts on a coherent quantitative cofactor hierarchy is, in the judgement of this review, the most clinically actionable finding in the literature. Relative to rest, aspirin reduced the median eliciting gluten dose by 83%, exercise by 63%, alcohol by 36%, and the combination of exercise and aspirin by 87%, with challenge positivity of 84%, 92%, 56% and 82% respectively. Severity followed a partially divergent ordering: exercise and aspirin approximately doubled to tripled the Sampson severity score, whereas alcohol left severity unchanged despite lowering the threshold. This dissociation between threshold effect and severity effect is mechanistically informative, suggesting that alcohol acts principally on absorption whereas exercise and NSAIDs additionally modify effector-cell reactivity or haemodynamic reserve. Registry data are consistent, with alcohol tripling the odds of severe wheat anaphylaxis (OR 3.23, 95% CI 1.31–8.83) — a finding that may reflect the frequent co-occurrence of alcohol with large evening carbohydrate loads rather than a direct pharmacodynamic effect.^{37,34,46}

Three clinical rules follow. First, aspirin and other cyclooxygenase inhibitors should be regarded as at least as dangerous as exercise for patients with WDEIA, and should be explicitly proscribed in the four-hour window surrounding culprit-food ingestion — a message that is frequently omitted from counselling, and that assumes particular importance in older patients receiving low-dose cardioprotective aspirin. Second, cofactor combinations are supra-additive in their threshold effect and should trigger the most conservative advice. Third, because 11% of patients have no identifiable cofactor and 48% react at rest at sufficient dose, absence of an obvious cofactor does not exclude the diagnosis.^{7,14,35,37,67}

Mechanistic Synthesis and Its Unresolved Contradiction

The dominant mechanistic model holds that cofactors increase gastrointestinal paracellular permeability, permitting intact allergen to reach submucosal and systemic effector cells. Direct evidence is substantial: immunoreactive gliadin appears in serum in parallel with symptoms during wheat-plus-exercise and wheat-plus-aspirin challenge but not with wheat alone; NSAIDs raise serum allergen levels in a manner dependent on cyclooxygenase-inhibition profile; the phenomenon is reproducible within subjects; premedication with a synthetic prostaglandin E1 analogue abolishes both the gliadin rise and the clinical reaction; and animal work confirms that aspirin increases paracellular absorption of intact and pepsin-digested gliadin with allergenicity preserved.^{10,14,15,42,52}

This model is nonetheless directly contradicted by a well-conducted prospective crossover study in twelve healthy volunteers in which cofactors did not substantially raise peak serum gliadin concentrations, although they markedly increased inter-individual variability and shifted peaks to later time points, and in which stool zonulin was unrelated to either cofactor exposure or peak gliadin. Those investigators proposed that gliadin absorption in health is largely cofactor-independent and that patients with WDEIA must possess a specific predisposition — hyperresponsive or damaged intestinal epithelium — or that alternative mechanisms predominate: exertional redistribution of splanchnic blood flow toward cutaneous and muscular mast-cell populations of distinct phenotype, exercise-induced plasma hyperosmolality and acidosis directly lowering the mast-cell and basophil degranulation threshold, and tissue transglutaminase-mediated allergen cross-linking. An EAACI position statement concluded that none of the proposed mechanisms currently possesses sufficient validity to be regarded as established, and called for a coordinated international research network.^{38,51,59}

A reconciling interpretation is available and is proposed here. The permeability effect is real but is neither necessary nor sufficient: it is demonstrable in healthy subjects, who do not react, and its magnitude varies more than one hundredfold between individuals, as shown by positive gliadin thresholds ranging from 15 to 2,111 pg/mL. Reaction therefore requires the conjunction of (i) a sufficient systemic allergen flux, itself the product of ingested dose and cofactor-modulated absorption; (ii) a sufficient burden of high-affinity allergen-specific IgE bound to effector cells; and

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(iii) a sufficiently low effector-cell activation threshold, which exercise lowers further through osmolar, thermal, adrenergic and pH-mediated effects. This tripartite model accounts for the observed dissociation between threshold and severity effects across cofactors, for the low reproducibility of challenge, for the existence of asymptomatic ω -5 gliadin sensitization, and for the absence of correlation between sIgE titre and reaction severity documented in three independent cohorts.^{25,35,38,50,59}

Diagnostic Strategy: From Provocation to Molecular Stratification

The historical reference standard — food ingestion followed by exercise challenge — is unsafe, resource-intensive and insensitive. Its insensitivity is quantified by the observation that four patients with previously negative conventional wheat challenges were confirmed on a gluten-based protocol, that only 66% of patients with a compelling history reacted in the largest challenge cohort, and that serum gliadin monitoring reclassified nine of nineteen challenge-negative patients. Its danger is quantified by the occurrence of hypotensive anaphylaxis during a standardized three-day protocol, and by the requirement for intravenous adrenaline in three of seven challenged children.^{23,25,32,34,39}

Three developments have progressively displaced challenge from the diagnostic pathway. The first is the substitution of gluten for whole wheat flour, which raises the deliverable dose of the relevant prolamins fraction and increased diagnostic yield to 100% in one protocol and 94.4% in another. The second is the systematic deployment of cofactor arms, which raised positivity from 48% at rest to 92% with exercise. The third, and most consequential for routine practice, is molecular diagnosis: combined gluten and ω -5 gliadin sIgE achieved 99.0% specificity in a 696-participant four-group Chinese study, permitting the investigators to propose formal diagnostic criteria that dispense with challenge — a proposal of particular importance in jurisdictions where research ethics committees will not sanction deliberate anaphylaxis provocation. Combined recombinant ω -5 gliadin and HMW-glutenin testing achieved 93.8% sensitivity with 92.9% specificity, and skin prick testing plus sIgE diagnosed 95% of FDEIA in a prospective multidisciplinary pathway.^{18,25,34,36,39,43}

Residual diagnostic gaps are concentrated in paediatrics and in seronegative disease. Omega-5 gliadin sIgE is less sensitive in children, and paediatric confirmation has required either challenge or the use of alternative components such as α/β gliadin, which was detectable in 100% of ω -5 gliadin-negative WDEIA patients in an adult series. Where component testing is negative and clinical suspicion persists, basophil activation testing offers allergen-resolved cellular confirmation, discriminating HWP-sensitized from conventional WDEIA with complete concordance and providing a validated surrogate endpoint in interventional trials.^{17,44,45,62}

Table 25. Proposed evidence-derived diagnostic algorithm

Step	Action	Evidence base
1	Structured history: temporal relation of food to exertion (4 h window), cofactor inventory (NSAID, alcohol, menses, infection, thermal stress), reproducibility, prior “idiopathic” episodes	Tanaka 1994; Kennard 2018; Du 2022
2	Acute-phase confirmation where feasible: paired serum tryptase at presentation and baseline	Chiang 2023
3	First-line molecular serology stratified by phenotype/geography — gliadin panel (ω -5 gliadin, HMW-glutenin $\pm$ α/β gliadin) or nsLTP panel (Pru p 3, Tri a 14, Art v 3, Jug r 3, Ara h 9, Cor a 8)	Matsuo 2008; Takahashi 2012; Romano 2012; Scala 2024; Aoki 2023
4	Skin prick testing with native gluten/gliadin preparations and prick-plus-prick with fresh suspect foods; avoid reliance on commercial wheat extract	Brockow 2015; Thongngarm 2020; Romano 1995
5	If steps 3–4 concordant with a compelling history → diagnosis established; proceed to management without challenge	Jiang 2018; Chiang 2023
6	If discordant or negative with persistent suspicion → titrated gluten challenge at rest, then with exercise, then with aspirin $\pm$ alcohol, under full resuscitation cover, with serum gliadin	Brockow 2015; Christensen 2018/2019; Kohno 2013

	monitoring	
7	Where challenge is contraindicated or refused → basophil activation testing with fractionated wheat preparations or suspect allergen	Chinuki 2012; Chinuki 2023; Aoki 2023
8	In post-oral-immunotherapy patients, treat a negative exercise provocation test as non-reassuring and maintain surveillance	Mukai 2026

Management: Comparative Effectiveness and Residual Risk

Two avoidance strategies compete. Complete elimination of the culprit food is the more effective for anaphylaxis prevention — 91.7% versus 87.0% in the largest followed cohort — and is uniquely effective against the intermittent low-grade urticaria that accompanies ordinary ingestion in some patients, whereas temporal separation of food from cofactors prevents anaphylaxis but not that urticaria. Against this, complete elimination imposes a substantial and lifelong nutritional and social burden, and there is a theoretical concern, articulated in the German-language dermatological literature, that complete wheat avoidance may promote loss of tolerance less favourably than continued regular cofactor-free consumption. In the absence of randomized comparison, the evidence supports a shared-decision approach: temporal separation with rigorous cofactor counselling as the default, escalating to complete elimination in patients with breakthrough reactions, intermittent urticaria on ordinary ingestion, unreliable cofactor control, or occupational exposure to unavoidable exertion.^{35,41,50,58}

Whichever strategy is adopted, residual risk is substantial and must be disclosed. Approximately one in five patients in the largest Chinese cohort and one in three in the largest UK cohort continued to react. Among the specific reasons documented are inadvertent ingestion of hidden wheat, unrecognized cofactors, and — in the oral-immunotherapy population — reliance on a falsely negative exercise provocation test, which preceded field reactions in 26.4% of children within one year. Universal prescription of an adrenaline auto-injector, structured emergency action planning, avoidance of solitary exercise, medical identification jewellery, and periodic re-training in device technique are therefore mandatory rather than discretionary. The importance of re-training is

quantified in the nsLTP literature, where only 47% of patients demonstrated correct auto-injector technique at final evaluation, and periodic education significantly reduced errors.^{35,41,49,65}

Pharmacological disease modification remains investigational. Misoprostol premedication abolished aspirin-provoked reactions in a proof-of-concept provocation study, a finding that is mechanistically coherent but has not been developed. Omalizumab produced a striking biomarker response in a phase 2 single-arm trial, with more than 80% of patients achieving basophil activation below 10% and 68.8% of these tolerating wheat, but the effect was not durable: after treatment cessation basophil activation and clinical reactivity returned progressively, reaching 46.7% positivity, and the investigators concluded explicitly that desensitization was not achieved. Case-level evidence supports omalizumab in refractory food-independent EIA, including a paediatric patient with nsLTP sensitization who failed dupilumab. Sublingual immunotherapy has been proposed but remains inadequately evidenced. No randomized controlled trial of any therapeutic intervention in FDEIA has been published.^{15,44,58,72}

The Hydrolysed Wheat Protein Episode as a Natural Experiment

The Japanese hydrolysed-wheat-protein outbreak, affecting more than two thousand individuals exposed to a single acid-hydrolysed wheat protein (Glupearl 19S) in a facial soap of which 46 million units were sold, provides evidence unobtainable by design. It demonstrates that (i) percutaneous and rhinoconjunctival exposure to a chemically modified food protein can establish clinically significant systemic food allergy in adults with no prior food-allergic history; (ii) the route of sensitization determines the molecular epitope profile, with IgE directed at α/β -, γ - and ω 1,2-gliadins rather than ω -5 gliadin, and with deamidated epitopes bound more avidly than native sequences — a direct consequence of acid hydrolysis converting glutamine to glutamic acid; (iii) the resulting clinical phenotype differs systematically, with facial angioedema predominating and haemodynamic compromise less frequent; and (iv) removal of the sensitizing exposure permits genuine immunological and clinical remission, quantified by Kaplan–Meier analysis in 110 patients — the only documented route to cure in this disorder.^{16,21,22,26,29,70}

The public-health implications extend well beyond wheat. Hydrolysed plant proteins are widely used as humectants in cosmetics globally, and the episode establishes a mechanism by

which cosmetic formulation can generate food anaphylaxis. It also identifies a host susceptibility factor, with angiotensin-converting-enzyme genotype distribution in 47 affected patients differing from a population reference cohort — biologically plausible given the role of ACE in kinin degradation and the reported association of ACE genotype with anaphylaxis to other elicitors, though requiring replication.^{22,27,29}

Under-Recognition, Delay and the Case for Systemic Intervention

Median diagnostic delay of 16 months to 2 years, with 29% of patients waiting more than five years, and — most tellingly — no improvement across calendar time in a large cohort spanning more than a decade, indicates a failure of systems rather than of individual clinicians. Three intervention points emerge from the data. In acute care, paired serum tryptase was obtained in only about one third of anaphylaxis presentations despite being elevated in 82.5% of those sampled, and adrenaline auto-injectors were under-prescribed. In specialist care, the recommendation that all adults presenting with anaphylaxis of unclear cause undergo ω -5 gliadin sIgE testing is supported by the finding that 10 of 67 ω -5 gliadin-positive patients had been labelled idiopathic. In schools and sports settings, awareness was documented at 31.1% among teachers and approximately 33% among school nurses, while seventeen of 167 nationally reported episodes occurred during lunch recess or physical education — the precise setting in which food ingestion and exertion are institutionally juxtaposed.^{3,7,8,30,35,41,43}

Comparison With Prior Syntheses

Two prior systematic reviews pooled 722 patients from 231 reports and characterized manifestations, culprit foods, triggering exercise and treatment response, and delineated three phenotypes — anaphylaxis with wheals and/or angioedema (80%), stand-alone wheals/angioedema (17%) and anaphylaxis without cutaneous features (4%) — reporting that patients with anaphylaxis were older at onset, less often atopic, more often challenge-positive, had a more restricted culprit-food spectrum and more often used adrenaline. Those syntheses provide descriptive richness that the present design-restricted review deliberately forgoes. However, 173 of the 231 included reports were single-patient case reports and a further 15 were case series, which precludes risk-of-bias appraisal, design-stratified analysis and certainty grading, and which inflates the apparent frequency

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of atypical presentations through publication bias. The present review, by restricting eligibility to analytical designs and by grading each outcome domain, yields more conservative but more defensible estimates — for example, it does not accept aggregate case-report proportions as prevalence estimates, and it grades treatment-effectiveness evidence as Low certainty despite its apparently impressive point estimates. A rapid evidence review with meta-analysis on risk factors for severe food-allergic reactions reached a concordant conclusion, finding that evidence for a cofactor effect on severity was generally lacking with FDEIA as the notable exception — precisely the domain in which the present review found Moderate-certainty evidence.^{53,54,55}

Strengths

The review's principal strengths are its prespecified restriction to analytical primary designs, which permits meaningful risk-of-bias appraisal and certainty grading; its fifteen-domain outcome architecture, which captures the full clinical pathway from epidemiology to prognosis; its dual risk-of-bias instrument appropriate to a mixed interventional–observational evidence base; its explicit integration of three previously separate literatures (East Asian gliadin, Northern European challenge, Mediterranean LTP); its derivation of a quantitative cofactor-potency hierarchy from directly comparable titration data; and its verification of every included reference through a persistent, publicly resolvable record identifier.

Implications for Practice

The evidence supports the following practice positions. All adults presenting with anaphylaxis of unclear cause should undergo ω-5 gliadin-specific IgE testing, with an nsLTP panel added where the clinical phenotype or geography suggests it. Component-resolved serology in molecular combination, interpreted alongside a structured temporal history, is sufficient for diagnosis in most adults, and challenge should be reserved for discordant cases. Cofactor counselling must be explicit, quantitative and comprehensive, encompassing NSAIDs — which are at least as potent as exercise — alcohol, menstruation, intercurrent infection and thermal extremes, and must state that cofactor combinations are supra-additive. Avoidance strategy should be individualized, with complete elimination reserved for patients with breakthrough reactions or intermittent urticaria on ordinary ingestion. Every patient requires an adrenaline auto-injector, a

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written emergency action plan, instruction to avoid solitary exercise, and periodic re-training in device technique. A negative provocation test, particularly after oral immunotherapy, must not be communicated as evidence of safety.

Implications for Research

Six priorities emerge. First, randomized or quasi-randomized cofactor-controlled challenge protocols with blinded outcome assessment are required to establish threshold and severity estimates free of expectancy bias. Second, paediatric molecular panels extending beyond ω -5 gliadin — α/β gliadin MM1, γ -gliadin, Tri a 14 — require prospective validation against challenge in children. Third, prospective multinational registries with standardized case definitions are needed to establish prevalence outside Japan and to characterize African, South Asian, Middle Eastern and Latin American phenotypes. Fourth, adequately powered randomized trials of omalizumab, and exploratory trials of prostaglandin E1 analogues, Bruton tyrosine kinase inhibitors and sublingual immunotherapy, are warranted given the durable failure of monotherapy withdrawal. Fifth, the contradiction between the permeability model and the negative healthy-volunteer crossover study requires resolution through mechanistic studies in patients rather than controls, incorporating simultaneous measurement of allergen flux, splanchnic haemodynamics, plasma osmolality, tissue transglutaminase activity and effector-cell activation. Sixth, health-services research is needed on interventions to reduce the diagnostic delay that has proved impervious to a decade of increasing awareness.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This systematic review of fifty analytical primary studies published between 1983 and 2026 supports the following conclusions.

1. **Exercise-induced allergy and food-dependent exercise-induced anaphylaxis constitute a single mechanistic continuum rather than distinct nosological entities.** Exercise functions as a threshold-lowering and severity-amplifying cofactor and is not obligatory:

reactions were elicited at rest in 37–48% of patients given sufficient allergen dose. Hypothesis H1 and H3 are supported.

2. **FDEIA is most accurately classified as a high-threshold, cofactor-dependent IgE-mediated food allergy.** The habitual dietary dose lies beneath the resting eliciting threshold but above the cofactor-reduced threshold.
3. **Two molecular archetypes dominate globally, with geographically determined frequency.** Omega-5 gliadin and high-molecular-weight glutenin predominate in East Asia, Northern Europe, the United Kingdom and Australia; non-specific lipid transfer proteins predominate in the Mediterranean basin, accounting for 66.3–78% of cases there. These two families are the only allergen groups clearly associated with exercise dependence. Hypothesis H2 is supported.
4. **Cofactors exert quantifiable, rank-ordered and supra-additive effects on eliciting threshold.** Relative to rest, threshold reduction was 87% for exercise plus aspirin, 83% for aspirin, 63% for exercise and 36% for alcohol; severity was approximately doubled by exercise and aspirin but unchanged by alcohol. Hypothesis H4 is supported.
5. **Component-resolved serology in molecular combination achieves diagnostic performance sufficient to obviate provocation challenge in most adults,** with combined recombinant ω -5 gliadin and HMW-glutenin achieving 93.8% sensitivity and 92.9% specificity, and combined gluten and ω -5 gliadin achieving 99.0% specificity. Performance is inferior in children. Hypothesis H6 is supported.
6. **Structured avoidance is highly but incompletely effective.** Complete elimination of the culprit food prevented further anaphylaxis in 91.7% and temporal separation in 87.0%, yet approximately one in five to one in three patients continued to react, and 26.4% of wheat-desensitized children with negative provocation tests reacted within one year. Hypothesis H5 is supported.

7. **Percutaneous sensitization to hydrolysed wheat protein produces a distinct, remediable phenotype**, characterized by female predominance, facial angioedema, non- ω -5-gliadin epitope recognition and genuine remission after exposure cessation.
8. **Diagnostic delay is severe, systemic and has not improved over time**, with median delays of 16 months to 2 years, 29% of patients waiting more than five years, and institutional awareness below one third in school settings.
9. **The overall certainty of evidence is Moderate for diagnostic-accuracy, cofactor-threshold, culprit-food, clinical-manifestation and care-quality domains, and Low for prevalence, demographic, biomarker, treatment and prognostic domains**. No randomized controlled trial of any intervention in this disorder has been published.

Recommendations

For clinical practice

1. Test ω -5 gliadin-specific IgE in every adult presenting with anaphylaxis of unclear cause, and add an nsLTP panel anchored on Pru p 3 where the phenotype or geography suggests lipid transfer protein syndrome.
2. Use native gluten or gliadin preparations for skin prick testing; do not rely on commercial whole-wheat extract, whose positivity rate was 9.1% in challenge-confirmed patients.
3. Reserve provocation challenge for cases in which molecular serology and history are discordant, and when performed, use titrated gluten with sequential cofactor arms under full resuscitation cover, with serum gliadin monitoring where available.
4. Counsel explicitly and quantitatively on the full cofactor inventory, emphasizing that non-steroidal anti-inflammatory drugs are at least as potent as exercise and that cofactor combinations are supra-additive.

5. Individualize the avoidance strategy: temporal separation with rigorous cofactor control as default; complete elimination for patients with breakthrough reactions, intermittent urticaria on ordinary ingestion, or unreliable cofactor control.
6. Prescribe an adrenaline auto-injector to every patient without exception, provide a written emergency action plan, advise against solitary exercise, recommend medical identification, and re-train device technique at every review.
7. Obtain paired acute and baseline serum tryptase in all suspected anaphylaxis presentations.
8. Do not communicate a negative provocation test as evidence of safety, particularly after oral immunotherapy.
9. Review cosmetic and personal-care product exposure in any adult with new-onset wheat allergy, especially women presenting with facial angioedema and contact urticaria.

For education and health systems

1. Incorporate FDEIA into mandatory training for school nurses, physical-education teachers, sports coaches and emergency-department staff, targeting the documented awareness deficit of approximately two thirds.
2. Establish institutional protocols separating school meals from physical-education classes by at least four hours where a diagnosed pupil is present.
3. Implement audit standards for paired tryptase sampling and adrenaline auto-injector prescription in emergency anaphylaxis care.
4. Strengthen regulatory surveillance of hydrolysed food proteins in cosmetics and personal-care products.

For research

1. Conduct randomized, blinded, cofactor-controlled challenge studies to derive unbiased threshold and severity estimates.
2. Prospectively validate paediatric molecular panels extending beyond ω -5 gliadin against challenge outcomes.
3. Establish prospective multinational registries with harmonized case definitions, prioritizing under-represented regions.
4. Undertake adequately powered randomized trials of omalizumab and exploratory trials of prostaglandin E1 analogues, Bruton tyrosine kinase inhibitors and sublingual immunotherapy.
5. Resolve the permeability controversy through patient-based mechanistic studies measuring allergen flux, splanchnic haemodynamics, osmolality, tissue transglutaminase activity and effector-cell activation simultaneously.
6. Evaluate health-services interventions designed to reduce the persistent diagnostic delay.

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