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ATOPIC DERMATITIS AS A PREDICTOR OF FOOD ALLERGY AND ASTHMA DEVELOPMENT IN CHILDHOOD

DERMATITE ATÓPICA COMO PREDITOR DO DESENVOLVIMENTO DE ALERGIA ALIMENTAR E ASMA NA INFÂNCIA

DERMATITIS ATÓPICA COMO PREDICTOR DEL DESARROLLO DE ALERGIA ALIMENTARIA Y ASMA EN LA INFANCIA

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ABSTRACT

Introduction: Atopic dermatitis often precedes food allergy and asthma, but the traditional atopic-march model is excessively deterministic when compared with the heterogeneous trajectories observed during childhood. The clinically relevant question is not whether every infant with atopic dermatitis will progress to other allergic diseases, but which combinations of age at onset, persistence, severity, barrier dysfunction, and allergic sensitization identify a substantially increased risk. Objective: To critically evaluate atopic dermatitis as a predictor of food allergy and asthma during childhood, quantify the prognostic gradient across clinical phenotypes, distinguish allergic sensitization from clinically confirmed allergy and preschool wheezing from asthma, and translate the available evidence into practical recommendations for surveillance and prevention. Methods: A structured narrative review was conducted using PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library. Prospective birth cohorts, population-based cohorts, trajectory analyses, systematic reviews, meta-analyses, and randomized prevention trials were prioritized. Outcomes included challenge-confirmed or clinically diagnosed food allergy, allergic sensitization, recurrent wheezing, and physician-diagnosed asthma. Evidence was synthesized according to the timing, persistence, and severity of atopic dermatitis, the presence of sensitization, and coexisting food allergy. Results and Discussion: In a population-based cohort of 4,453 one-year-old infants, eczema was associated with challenge-confirmed food allergy (odds ratio [OR] 6.2; 95% confidence interval [CI] 4.9–7.9), peanut allergy (OR 11.0; 95% CI 6.6–18.6), and egg allergy (OR 5.8; 95% CI 4.6–7.4). A meta-analysis of 39 publications involving 458,810 participants found that atopic dermatitis predicted subsequent asthma (relative risk [RR] 2.16; 95% CI 1.88–2.48), with a greater risk for persistent disease (RR 3.36) than for transient disease (RR 1.52). In the Canadian Healthy Infant Longitudinal Development cohort, atopic dermatitis without allergic sensitization did not predict asthma, whereas atopic dermatitis accompanied by sensitization was strongly predictive (RR 7.04; 95% CI 4.13–11.99). Early-onset and

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persistent phenotypes, moderate-to-severe disease, and coexisting food allergy consistently identified the highest-risk trajectories. Early peanut and cooked-egg introduction reduced food allergy in randomized trials, whereas primary prevention based exclusively on emollient use did not reliably prevent atopic dermatitis or downstream allergic disease. Conclusion: Atopic dermatitis is a clinically useful marker of risk for food allergy and asthma, but it is not a deterministic precursor. Prediction improves substantially when age at onset, persistence, severity, objective allergic sensitization, and coexisting clinical food allergy are considered together. Infants with early moderate-to-severe atopic dermatitis require optimized skin treatment, careful history-based allergy assessment, and timely introduction of allergenic foods under risk-appropriate supervision. Indiscriminate food panels and empirical elimination diets should be avoided. The available evidence is insufficient to conclude that conventional treatment of atopic dermatitis independently prevents asthma.

Keywords: Dermatitis. Atopic. Food Hypersensitivity. Asthma. Child.

RESUMO

Introdução: A dermatite atópica frequentemente precede a alergia alimentar e a asma, mas o modelo tradicional de marcha atópica é excessivamente determinístico quando comparado com as trajetórias heterogêneas observadas durante a infância. A questão clinicamente relevante não é se todo lactente com dermatite atópica progredirá para outras doenças alérgicas, mas quais combinações de idade de início, persistência, gravidade, disfunção de barreira e sensibilização alérgica identificam um risco substancialmente aumentado. Objetivo: Avaliar criticamente a dermatite atópica como preditor de alergia alimentar e asma durante a infância, quantificar o gradiente prognóstico entre fenótipos clínicos, distinguir sensibilização alérgica de alergia clinicamente confirmada e sibilância pré-escolar de asma, e traduzir as evidências disponíveis em recomendações práticas para vigilância e prevenção. Métodos: Uma revisão narrativa estruturada foi conduzida usando PubMed/MEDLINE, Scopus, Web of Science e a Cochrane Library. Coortes de nascimento prospectivas, coortes populacionais, análises de trajetória, revisões sistemáticas, meta-análises e ensaios de prevenção randomizados foram priorizados. Os desfechos incluíram alergia alimentar confirmada por desafio ou diagnosticada clinicamente, sensibilização alérgica, sibilância recorrente e asma diagnosticada por médico. A evidência foi sintetizada de acordo com o momento, persistência e gravidade da dermatite atópica, a presença de sensibilização e alergia alimentar coexistente. Resultados e Discussão: Em uma coorte populacional de 4.453 lactentes de um ano de idade, o eczema foi associado com alergia alimentar confirmada por desafio (razão de chances [OR] 6,2; intervalo de confiança de 95% [IC] 4,9–7,9), alergia a amendoim (OR 11,0; IC 95% 6,6–18,6) e alergia a ovo (OR 5,8; IC 95% 4,6–7,4). Uma meta-análise de 39 publicações envolvendo 458.810 participantes constatou que a dermatite atópica predisse asma subsequente (risco relativo [RR] 2,16; IC 95% 1,88–2,48), com maior risco para doença persistente (RR 3,36) do que para doença transitória (RR 1,52). Na coorte Canadian Healthy Infant Longitudinal Development, dermatite atópica sem sensibilização alérgica não predisse asma, enquanto dermatite atópica acompanhada de sensibilização foi fortemente preditiva (RR 7,04; IC 95% 4,13–11,99). Os fenótipos de início precoce e persistentes, doença moderada a grave e alergia alimentar coexistente identificaram consistentemente as trajetórias de maior risco. A introdução precoce de amendoim e ovo cozido reduziram alergia alimentar em ensaios randomizados, enquanto a prevenção primária baseada exclusivamente no uso de emolientes não preveniu de forma confiável a dermatite atópica ou doença alérgica subsequente. Conclusão: A dermatite atópica é um marcador clinicamente útil de risco para alergia alimentar e asma, mas não é

um precursor determinístico. A predição melhora substancialmente quando idade de início, persistência, gravidade, sensibilização alérgica objetiva e alergia alimentar clínica coexistente são consideradas em conjunto. Lactentes com dermatite atópica moderada a grave de início precoce requerem tratamento otimizado da pele, avaliação cuidadosa da alergia baseada em história clínica e introdução oportuna de alimentos alergênicos sob supervisão apropriada ao risco. Painéis alimentares indiscriminados e dietas de eliminação empíricas devem ser evitados. A evidência disponível é insuficiente para concluir que o tratamento convencional da dermatite atópica previne independentemente a asma.

Palavras-chave: Dermatite. Atópica. Hipersensibilidade Alimentar. Asma. Criança.

RESUMEN

Introducción: La dermatitis atópica frecuentemente precede a la alergia alimentaria y al asma, pero el modelo tradicional de marcha atópica es excesivamente determinista cuando se compara con las trayectorias heterogéneas observadas durante la infancia. La pregunta clínicamente relevante no es si todo lactante con dermatitis atópica progresará a otras enfermedades alérgicas, sino qué combinaciones de edad de inicio, persistencia, gravedad, disfunción de la barrera y sensibilización alérgica identifican un riesgo sustancialmente aumentado. Objetivo: Evaluar críticamente la dermatitis atópica como predictor de alergia alimentaria y asma durante la infancia, cuantificar el gradiente pronóstico entre fenotipos clínicos, distinguir la sensibilización alérgica de la alergia clínicamente confirmada y la sibilancia preescolar del asma, y traducir la evidencia disponible en recomendaciones prácticas para vigilancia y prevención. Métodos: Se realizó una revisión narrativa estructurada utilizando PubMed/MEDLINE, Scopus, Web of Science y la Cochrane Library. Se priorizaron cohortes prospectivas de nacimiento, cohortes basadas en la población, análisis de trayectorias, revisiones sistemáticas, metaanálisis y ensayos de prevención aleatorizados. Los resultados incluyeron alergia alimentaria confirmada por desafío o diagnosticada clínicamente, sensibilización alérgica, sibilancia recurrente y asma diagnosticada por médico. La evidencia fue sintetizada de acuerdo con el momento, la persistencia y la gravedad de la dermatitis atópica, la presencia de sensibilización y la alergia alimentaria coexistente. Resultados y Discusión: En una cohorte poblacional de 4.453 lactantes de un año de edad, el eccema se asoció con alergia alimentaria confirmada por desafío (razón de momios [OR] 6,2; intervalo de confianza del 95% [IC] 4,9–7,9), alergia al cacahuete (OR 11,0; IC 95% 6,6–18,6) y alergia al huevo (OR 5,8; IC 95% 4,6–7,4). Un metaanálisis de 39 publicaciones que incluyeron a 458.810 participantes encontró que la dermatitis atópica predijo asma posterior (riesgo relativo [RR] 2,16; IC 95% 1,88–2,48), con mayor riesgo para enfermedad persistente (RR 3,36) que para enfermedad transitoria (RR 1,52). En la cohorte Canadian Healthy Infant Longitudinal Development, la dermatitis atópica sin sensibilización alérgica no predijo asma, mientras que la dermatitis atópica acompañada de sensibilización fue fuertemente predictiva (RR 7,04; IC 95% 4,13–11,99). Los fenotipos de inicio temprano y persistentes, la enfermedad moderada a grave y la alergia alimentaria coexistente identificaron consistentemente las trayectorias de mayor riesgo. La introducción temprana de cacahuete y huevo cocido redujeron la alergia alimentaria en ensayos aleatorizados, mientras que la prevención primaria basada exclusivamente en el uso de emolientes no previno de manera confiable la dermatitis atópica o la enfermedad alérgica posterior. Conclusión: La dermatitis atópica es un marcador clínicamente útil de riesgo para alergia alimentaria y asma, pero no es un precursor determinista. La predicción mejora sustancialmente cuando se consideran juntos la edad de inicio, la persistencia, la gravedad, la sensibilización alérgica objetiva y la alergia alimentaria clínica coexistente. Los lactantes

con dermatitis atópica moderada a grave de inicio temprano requieren tratamiento optimizado de la piel, evaluación cuidadosa de la alergia basada en la historia clínica e introducción oportuna de alimentos alergénicos bajo supervisión apropiada al riesgo. Se deben evitar los paneles alimentarios indiscriminados y las dietas de eliminación empíricas. La evidencia disponible es insuficiente para concluir que el tratamiento convencional de la dermatitis atópica previene independientemente el asma.

Palabras clave: Dermatitis. Atópica. Hipersensibilidad Alimentaria. Asma. Niño.

1 INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by pruritus, xerosis, impairment of the epidermal barrier, and age-dependent clinical morphology. It commonly begins during infancy, when the epidermal barrier and immune-tolerance mechanisms are still developing. Contemporary evidence characterizes AD as a heterogeneous disorder produced by interactions among genetic susceptibility, epithelial dysfunction, immune dysregulation, microbial alterations, and environmental exposures.[1]

The association between AD, food allergy, asthma, and allergic rhinitis has historically been described as the atopic march. According to this model, eczema develops during infancy, followed by food allergy and subsequently by respiratory allergic disease. Although this sequence occurs in some children, many experience overlapping disorders, incomplete or reversed sequences, spontaneous remission, or AD without any subsequent allergic condition.[2]

The more clinically accurate concept is therefore one of atopic multimorbidity with multiple possible trajectories rather than an inevitable unidirectional march. AD is a marker of increased probability, not a prediction that every affected child will develop food allergy or asthma.[2]

Epidermal-barrier impairment provides a plausible biological mechanism connecting early skin disease to systemic allergic sensitization. Reduced structural proteins, abnormal epidermal lipids, increased transepidermal water loss, inflammation, scratching, and microbial dysbiosis can increase cutaneous exposure to environmental and food proteins.[3]

Epithelial alarmins and type 2 cytokine signaling may promote immunoglobulin E production and allergic sensitization. Similar epithelial and immunological susceptibility may also affect the airways, contributing to bronchial inflammation and respiratory disease.[3]

Shared susceptibility complicates causal interpretation. Filaggrin variants, parental atopy, sex, ancestry, smoke exposure, respiratory infections, microbiome development, feeding practices, and socioeconomic or healthcare-related characteristics may predispose children to both AD and later allergic disease. AD may therefore function as a causal contributor, a marker of a common biological endotype, or both.[4]

Food allergy requires particularly careful definition in children with AD. Food sensitization refers to detectable food-specific immunoglobulin E or a positive skin-prick test, whereas clinical food allergy requires reproducible symptoms following exposure, ideally confirmed through an oral food challenge when the diagnosis remains uncertain.[5]

Children with AD frequently demonstrate asymptomatic sensitization. Broad and indiscriminate testing can consequently produce false-positive diagnoses, unnecessary dietary avoidance, nutritional impairment, family anxiety, and potentially the loss of established oral tolerance.[5]

The dual-allergen-exposure hypothesis provides a coherent explanation for the strong association between early AD and food allergy. Exposure to food proteins through inflamed skin may promote allergic sensitization, whereas timely oral exposure through the gastrointestinal tract may favor immune tolerance.[6]

This hypothesis is supported by epidemiological observations, experimental biology, environmental food-protein studies, and randomized trials of early oral introduction. It does not imply that every exacerbation of AD is food-induced or that treatment of the epidermal barrier alone prevents food allergy.[6]

The association between AD and asthma also varies substantially among phenotypes. A meta-analysis of 39 publications involving 458,810 participants found an overall RR of 2.16 for subsequent asthma. The risk was 3.36 among children with persistent AD and 1.52 among those with transient disease. Severe AD was also associated with greater risk than mild or moderate disease.[7]

These gradients demonstrate that disease duration and severity provide more prognostic information than a simple binary history of eczema. Early-onset, persistent, severe, and sensitized AD should not be interpreted in the same manner as mild, transient, and nonsensitized disease.[7]

Relative risk must also be considered alongside absolute risk. AD is associated with several atopic comorbidities, but many children with mild and transient disease never develop food allergy or asthma. Even a large relative estimate may represent only a modest absolute increase when the baseline risk is low.[8]

A clinically useful assessment must therefore distinguish association from prediction, prediction from causation, and risk-stratified surveillance from indiscriminate screening. The objective is not to label every infant with eczema as destined to develop allergy, but to recognize combinations of clinical characteristics that justify earlier preventive or diagnostic intervention.[8]

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

To determine how accurately childhood atopic dermatitis predicts subsequent food allergy and asthma and to identify the phenotypic characteristics that meaningfully modify this risk.

2.2 SECONDARY OBJECTIVES

1. To quantify the associations between early-onset, persistent, and severe AD and clinically diagnosed or challenge-confirmed food allergy.
2. To compare the risk of subsequent asthma among transient, persistent, early-onset, late-onset, sensitized, and nonsensitized AD phenotypes.
3. To distinguish food sensitization from clinical food allergy and recurrent preschool wheezing from later physician-diagnosed asthma.
4. To examine whether coexisting food allergy, epidermal-barrier dysfunction, filaggrin variation, sex, familial atopy, and environmental factors improve risk stratification.
5. To evaluate whether early allergen introduction, skin-barrier interventions, or improved AD control modify subsequent allergic outcomes.
6. To develop a practical clinical framework for counseling, diagnostic testing, dietary decisions, longitudinal follow-up, and specialist referral.

3 METHODOLOGY

3.1 STUDY DESIGN

This article was developed as a structured narrative review. This design was selected because the question is both prognostic and mechanistic and the available evidence includes prospective birth cohorts, population-based studies, latent-class trajectory analyses, systematic reviews, meta-analyses, claims databases, and randomized prevention trials with heterogeneous definitions and follow-up periods.

3.2 INFORMATION SOURCES AND SEARCH STRATEGY

PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library were searched from database inception through August 2026. Search terms included atopic dermatitis, eczema, infantile eczema, disease phenotype, trajectory, persistence, severity,

food allergy, food sensitization, oral food challenge, peanut, egg, asthma, wheezing, atopic march, allergic multimorbidity, filaggrin, transepidermal water loss, prediction, cohort, meta-analysis, and prevention.

Reference lists and forward citations of pivotal studies and contemporary reviews were also examined.

3.3 ELIGIBILITY AND EVIDENCE PRIORITIZATION

Human studies were prioritized when AD was documented before or during the ascertainment of food allergy or asthma and when age at onset, persistence, severity, sensitization, or coexisting food allergy was reported.

Prospective cohorts and population-based samples were assigned greater weight than clinic-only case series. For preventive interventions, randomized trials of early oral allergen introduction and skin-barrier intervention were prioritized. Cross-sectional studies were used only when they clarified relevant diagnostic or mechanistic distinctions.

3.4 OUTCOMES AND DEFINITIONS

The hierarchy for food-allergy ascertainment consisted of oral-food-challenge confirmation, a convincing immediate reaction accompanied by objective sensitization, physician diagnosis, and parental report. Sensitization alone was analyzed separately.

Asthma was preferentially defined after the preschool period using physician diagnosis, validated questionnaires, medication patterns, or objective respiratory testing. Recurrent preschool wheezing was not automatically classified as asthma.

AD phenotypes were categorized according to age at onset, persistence or remission, clinical severity, treatment requirements, and the presence of allergic sensitization.

3.5 DATA EXTRACTION AND SYNTHESIS

The extracted variables included study design, population, sample size, AD phenotype, comparator, outcome definition, adjusted effect estimates, confidence intervals, follow-up duration, and principal methodological limitations.

Because of substantial heterogeneity, the results were not statistically re-pooled. Evidence was synthesized according to clinical outcome and the observed risk gradient, with particular attention to temporality, reverse causation, confounding, attrition, repeated measurements, multiple comparisons, and the distinction between relative and absolute risk.

3.6 CERTAINTY FRAMEWORK

Certainty was evaluated narratively according to study design, consistency, statistical precision, directness, phenotype or dose gradient, and risk of bias.

Observational associations were not interpreted as proof that treating AD prevents subsequent allergic disease. Randomized allergen-introduction trials were considered evidence for food-allergy prevention rather than direct evidence that controlling established AD prevents asthma.

4 RESULTS

4.1 EVIDENCE LANDSCAPE

The principal evidence included population-based infant studies, longitudinal birth cohorts with repeated AD measurements, national administrative datasets, cross-cohort trajectory analyses, contemporary systematic reviews, meta-analyses, and randomized prevention trials.

Across study designs, the direction of association was relatively consistent, but the magnitude of risk varied substantially. Early onset, persistence, greater severity, objective sensitization, and coexisting clinical food allergy repeatedly identified children at higher risk.

Mild and transient AD without sensitization carried substantially less risk and did not behave as a deterministic precursor of allergic disease.

Associations with food allergy were strongest when the outcome was confirmed through oral challenge and AD was documented during infancy. Asthma estimates were most informative when follow-up extended into school age and analyses incorporated allergic sensitization and longitudinal phenotype trajectories.

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Table 1

Principal prognostic studies of atopic dermatitis, food allergy, and asthma

Study	Design and sample	AD phenotype	Outcome	Quantitative result	Interpretation
Martin et al., 2015[9]	Population-based HealthNuts cohort; 4,453 infants at one year	Eczema, age at onset, and prescribed topical treatment	Challenge-confirmed peanut, egg, or sesame allergy	Any food allergy OR 6.2 (95% CI 4.9–7.9); peanut allergy OR 11.0 (6.6–18.6); egg allergy OR 5.8 (4.6–7.4)	Strong absolute and relative gradient with high-quality allergy confirmation
Roduit et al., 2017[10]	PASTURE birth cohort; 1,038 children	Early transient, early persistent, late, or absent/infrequent AD	Food allergy, asthma, and allergic rhinitis	Early persistent AD predicted asthma: adjusted OR 2.87 (95% CI 1.31–6.31)	Timing and persistence distinguished high- and low-risk trajectories
Tran et al., 2018[11]	CHILD prospective cohort; 2,311 children	AD with or without sensitization at one year	Asthma and food allergy by three years	AD without sensitization: asthma RR 0.46 (95% CI 0.11–1.93); AD with sensitization: RR 7.04 (4.13–11.99)	Sensitization substantially changed the prognostic meaning of AD
Kotsapas et al., 2022[12]	Manchester Asthma and Allergy Study; 959 evaluable participants	Infant eczema and early sensitization	Peanut allergy and later wheezing or asthma	Infant eczema predicted peanut allergy: OR 4.4 (95% CI 1.5–13.2); egg sensitization at three years: OR 9.7 (3.3–29.9)	Combined eczema and sensitization identified a particularly high-risk group
Jung et al., 2022[13]	Korean longitudinal cohort; 1,579 children	AD with or without coexisting food allergy	Wheezing, asthma, and rhinitis at 6–8 years	AD with food allergy versus AD alone: adjusted OR 8.09 (95% CI 2.54–25.76) for recent wheezing at eight years	Coexisting food allergy identified a high-risk respiratory trajectory
Miltner et al., 2024[14]	Dutch population cohort; 6,852 participants	Age-of-onset and persistence phenotypes	Likely food allergy and asthma	Very early persistent eczema: adjusted OR 10.4 for likely food allergy and 4.1 for asthma	Very early persistent disease demonstrated the highest multimorbidity risk
Choi et al., 2025[15]	US MarketScan cohort; 27,228 infants with AD and 55,174 controls	AD diagnosed before one year; severity and family history	Food allergy, asthma, rhinitis, and complete atopic triad	Food allergy: 16.00% versus 2.27%; asthma: 19.21% versus 8.65%; severe AD HR 3.16 for the complete triad	Demonstrated clinically relevant absolute burden, but claims data are vulnerable to surveillance bias

Study	Design and sample	AD phenotype	Outcome	Quantitative result	Interpretation
Sitarik et al., 2025[16]	Nine US birth cohorts; 5,314 children	Transient early, early recurrent, persistent, late, or minimal/no AD	Food allergy, asthma, and allergic rhinitis	Food-allergy adjusted ORs 2.15–2.43 for early phenotypes; persistent AD predicted asthma with adjusted OR 2.31	Cross-cohort analysis confirmed phenotype-specific risk
Kuniyoshi, 2026[17]	Japanese national birth cohort; 23,767 children followed to 12 years	Early transient, early persistent, toddler persistent, late, or no AD	Food-allergy-related healthcare visits	Adjusted ORs approximately 2.3 for early transient, early persistent, and toddler-persistent phenotypes	Early skin disease predicted later food-allergy-related care across different trajectories
Islam et al., 2026[18]	Systematic review and meta-analysis; 190 studies and approximately 2.8 million participants	First-year AD, severity, transepidermal water loss, and filaggrin variants	Childhood IgE-mediated food allergy	First-year AD OR 3.88; absolute risk difference 12.0%; high transepidermal water loss OR 3.36; filaggrin variation OR 1.93	Comprehensive synthesis supporting a graded relationship between barrier dysfunction and food allergy

AD: atopic dermatitis; CHILD: Canadian Healthy Infant Longitudinal Development; CI: confidence interval; HR: hazard ratio; OR: odds ratio; RR: relative risk.
Source: Prepared by the authors.

5 RESULTS AND DISCUSSION

5.1 INFANT ECZEMA AND CHALLENGE-CONFIRMED FOOD ALLERGY

The clearest prognostic evidence derives from the population-based HealthNuts cohort, in which one-year-old infants underwent standardized assessment and sensitized participants were evaluated through oral food challenge. Eczema was associated with a sixfold increase in any challenge-confirmed peanut, egg, or sesame allergy, an 11-fold increase in peanut allergy, and almost a sixfold increase in egg allergy.[9]

Approximately one in five infants with eczema had one of these food allergies, compared with approximately one in 25 infants without eczema. These findings convert the relative association into a clinically meaningful absolute difference.[9]

Risk increased sharply when eczema began early and required medical treatment. Among infants whose eczema began before three months of age and required a prescribed topical corticosteroid, 50.8% had challenge-confirmed food allergy by one year.[9]

This estimate should not be generalized to every infant with mild eczema. It identifies a specific high-risk phenotype in which delayed or nonspecific dietary counseling may be inadequate and preventive assessment is time sensitive.

The diagnostic standard is central to interpretation. AD can increase total and food-specific immunoglobulin E without producing reproducible symptoms. Sensitization is consequently more prevalent than genuine food allergy.

The HealthNuts findings are more clinically applicable than results from clinic-based studies that define food allergy exclusively according to a positive laboratory or skin test.[9]

5.2 TIMING AND PERSISTENCE AS PROGNOSTIC CHARACTERISTICS

The PASTURE cohort classified children into early transient, early persistent, late, and absent or infrequent AD phenotypes instead of using a simple binary exposure. Early persistent AD predicted subsequent asthma with an adjusted OR of 2.87, while both early phenotypes were strongly associated with food allergy.[10]

Late-onset disease did not demonstrate the same food-allergy pattern. This finding supports the existence of a developmental period in which epidermal-barrier disruption overlaps with initial environmental and oral exposure to food antigens.[10]

Persistence may integrate several latent characteristics, including sustained barrier dysfunction, repeated inflammation, cumulative severity, treatment burden, microbial disturbance, and a stable type 2 inflammatory endotype.

It may therefore provide greater prognostic information than severity recorded during a single medical consultation. Persistence is also observable through repeated clinical follow-up, making trajectory-based counseling more useful than a static diagnosis.[10]

Trajectory analyses remain vulnerable to methodological limitations. Class assignment depends on the number and timing of assessments, parental reporting, missing observations, treatment accessibility, and the statistical model selected.

The reproducibility of early-persistent risk across different cohorts is reassuring, but identical phenotype labels should not be assumed to represent exactly the same population in every study.

5.3 ALLERGIC SENSITIZATION AND THE PROGNOSTIC MEANING OF ATOPIC DERMATITIS

In the CHILD cohort, AD at one year did not uniformly predict subsequent asthma. AD without sensitization had an imprecise RR of 0.46, whereas AD accompanied by sensitization had an RR of 7.04 for asthma by three years of age.[11]

A strong interaction was also identified for food allergy. The combination of epidermal disease and objective sensitization therefore provided more information than either characteristic considered independently.[11]

This finding may explain part of the variation among previous studies. Cohorts containing greater proportions of sensitized, severe, or persistent AD will report stronger respiratory associations than cohorts composed predominantly of mild and nonsensitized disease.

Sensitization can function as a marker of common biological susceptibility and as a potential mediator between cutaneous antigen exposure and subsequent respiratory allergy. Statistical adjustment for sensitization may therefore alter the scientific question being evaluated.[11]

Clinically, the findings support selective rather than universal allergy testing. Testing is most useful when the child has a history of an immediate reaction, persistent moderate-to-severe AD despite optimized treatment, or requires a decision regarding supervised food introduction.

The evidence does not support broad food or inhalant panels for every child with mild and controlled eczema.

5.4 PEANUT ALLERGY AND EARLY SENSITIZATION

The Manchester Asthma and Allergy Study evaluated peanut allergy in a deeply characterized birth cohort. Infant eczema independently predicted peanut allergy, with an OR of 4.4, while egg sensitization at three years demonstrated an OR of 9.7.[12]

Early eczema is therefore an accessible clinical marker, whereas combined sensitization data may identify a smaller subgroup with considerably greater risk.

Only 30 participants had confirmed peanut allergy, resulting in wide confidence intervals and limiting the complexity of multivariable analyses. Nevertheless, the results are consistent with the dual-exposure hypothesis.

Impaired skin may permit sensitization to environmental peanut proteins, while delayed oral exposure may eliminate an opportunity to establish tolerance. The association with later wheezing does not establish that peanut allergy itself causes asthma or increases its severity.[12]

Prediction should lead to prevention rather than avoidance by default. When eczema indicates increased peanut-allergy risk, the objective should be to determine how peanut can be introduced safely and promptly.

Specialist evaluation may be necessary in children with severe eczema, previous reactions, or strongly positive testing. Prolonged avoidance while waiting for indiscriminate screening may increase rather than decrease the opportunity for allergic sensitization.

5.5 COEXISTING FOOD ALLERGY AND RESPIRATORY RISK

In the Korean longitudinal cohort, AD accompanied by food allergy was associated with approximately eightfold greater adjusted odds of recent wheezing at eight years than AD without food allergy. The combination of early-onset persistent AD and food allergy demonstrated the most distinctive trajectory of school-age wheezing and allergic rhinitis.[13]

These findings support allergic multimorbidity as a stronger prognostic unit than either diagnosis considered separately.

Several mechanisms may explain this relationship, including a shared high-type-2 inflammatory endotype, more extensive barrier dysfunction, broader allergic sensitization, increased susceptibility to viral wheezing, or early airway inflammation.

Food allergy may function primarily as a marker of severity rather than as the direct cause of asthma. Avoidance of a confirmed allergen is essential for preventing food reactions, but there is no evidence that avoidance reverses the underlying respiratory trajectory.[13]

The reported effect estimate was large but imprecise. It should justify closer respiratory surveillance, attention to recurrent wheezing, avoidance of tobacco-smoke exposure, and timely asthma evaluation rather than preemptively diagnosing an asymptomatic child with asthma.

Prognostic awareness should reduce diagnostic delay without recording disease before clinical diagnostic criteria are satisfied.

5.6 ALLERGIC MULTIMORBIDITY AND VERY EARLY PERSISTENT ECZEMA

A Dutch population cohort evaluated the relationship between eczema phenotypes, food allergy, asthma, and hay fever. Very early persistent eczema beginning before six months and continuing afterward was associated with an adjusted OR of 10.4 for likely food allergy and 4.1 for asthma compared with children who never developed eczema.[14]

Later and transient phenotypes demonstrated less allergic multimorbidity, confirming a gradient rather than a binary progression.

A child with persistent early disease experiences longer cumulative exposure to barrier impairment and inflammation and may also have greater genetic susceptibility. This phenotype can therefore function as a composite clinical biomarker.

Food allergy in this cohort was assessed through questionnaires. The estimate may consequently include sensitization, food intolerance, or parental attribution rather than challenge-confirmed disease.[14]

The practical implication is that risk should be reassessed repeatedly. An infant whose mild eczema resolves may move toward a lower-risk trajectory. An infant whose disease remains active despite appropriate treatment accumulates evidence supporting targeted allergy assessment.

Prognosis should evolve with the phenotype instead of being permanently determined by the first episode of eczema.

5.7 ABSOLUTE BURDEN IN A LARGE HEALTHCARE POPULATION

The MarketScan study compared 27,228 infants diagnosed with AD before one year of age with 55,174 matched controls. Food allergy was recorded in 16.00% of children with AD and 2.27% of controls, while asthma was recorded in 19.21% and 8.65%, respectively.[15]

Approximately 10.6% of children with AD developed the complete triad of food allergy, asthma, and allergic rhinitis, compared with 0.71% of controls. These absolute differences communicate the disease burden more clearly than relative estimates alone.[15]

Within the AD cohort, severe disease, male sex, and documented family history increased the risk of the complete atopic triad. Severe AD was associated with an HR of 3.16, while family history was associated with HRs exceeding 3.40.[15]

These variables are available during routine clinical care and can be incorporated into anticipatory counseling. Family history, however, may be incompletely recorded in administrative datasets.

Administrative diagnoses are influenced by healthcare access and surveillance. Infants with AD have more medical encounters and therefore more opportunities to receive asthma or food-allergy codes.

Claims data cannot consistently distinguish challenge-confirmed allergy from presumed allergy or persistent school-age asthma from early wheezing. Large sample size increases precision but cannot fully compensate for phenotype misclassification.[15]

5.8 CROSS-COHORT CONFIRMATION OF PHENOTYPE-SPECIFIC RISK

The Environmental Influences on Child Health Outcomes and Children's Respiratory and Environmental Workgroup collaboration harmonized repeated AD data from nine United States birth cohorts. The investigators identified transient early, early recurrent, persistent, late-onset, and minimal or absent AD phenotypes.[16]

Early phenotypes predicted food allergy, with adjusted ORs between 2.15 and 2.43. Persistent AD predicted asthma with an adjusted OR of 2.31.[16]

The temporal pattern was biologically coherent. Early epidermal disease was most strongly associated with food allergy, while sustained disease was more strongly associated with subsequent respiratory disease.

Combining individual-level longitudinal information from multiple cohorts provides greater generalizability than single-center clinical studies. It also introduces harmonization challenges because questionnaires, examination intervals, diagnostic definitions, and population characteristics differ among studies.[16]

The phenotype structure should therefore be interpreted as a reproducible general pattern rather than as a universal bedside classification algorithm.

The most transferable conclusion is that a history of ever having AD omits important prognostic information. Medical records should document at least the age at onset, persistence, current activity, treatment requirements, and history of food reactions or sensitization.

These characteristics can support individualized counseling even before a formal prediction model is validated.

5.9 LONG-TERM TRAJECTORY EVIDENCE

A Japanese national birth cohort followed 23,767 children from infancy until 12 years of age and identified five eczema trajectories. Early transient, early persistent, and toddler-

persistent phenotypes each demonstrated adjusted ORs of approximately 2.3 for subsequent food-allergy-related healthcare visits.[17]

Late-onset eczema had a smaller OR of 1.42. These results support the importance of early barrier disease in a different healthcare and cultural setting.

Similar estimates for early transient and persistent phenotypes caution against assuming that remission completely eliminates previous risk. Sensitization may develop during a relatively short period of early barrier impairment before the skin improves.

Conversely, late-onset AD may develop after the principal period for establishing oral food tolerance and may therefore demonstrate a weaker relationship with food allergy.[17]

The outcome was based on parental reports of healthcare use for food allergy rather than systematic oral challenge. Cultural differences in food introduction, common allergens, diagnostic access, and parental reporting can influence absolute risk.

The trajectory findings are informative but should not be used as exact diagnostic probabilities in unrelated populations.

5.10 INTEGRATED FOOD-ALLERGY RISK

A comprehensive systematic review and meta-analysis published in 2026 included 190 studies and approximately 2.8 million participants. AD during the first year was associated with food allergy, with an OR of 3.88 and an absolute risk difference of 12 percentage points.[18]

Elevated transepidermal water loss and filaggrin variants were also identified as risk factors. Challenge-confirmed food-allergy incidence across population-based studies was approximately 4.7%, providing a useful baseline for interpreting higher-risk estimates.[18]

The combination of clinical AD, physiological barrier impairment, and genetic susceptibility supports a graded biological model. None of these factors is completely specific, and their combination may be more predictive than any isolated characteristic.

A future prediction model could incorporate age at onset, disease severity, persistence, transepidermal water loss, sensitization, family history, and genotype. Such a tool would require external validation and evidence that its use improves clinical outcomes.

Meta-analysis cannot eliminate heterogeneity in definitions. Some studies used sensitization or parental report as the food-allergy outcome, whereas incidence estimates generally required oral challenge.

The pooled evidence supports AD as a strong population-level predictor but does not justify diagnosing food allergy solely from the presence of eczema.[18]

5.11 PREVENTION THROUGH EARLY ORAL ALLERGEN INTRODUCTION

The Learning Early About Peanut Allergy (LEAP) trial randomized 640 infants between four and 11 months of age with severe eczema, egg allergy, or both to peanut consumption or avoidance. At five years, peanut allergy occurred in 17.2% of the avoidance group and 3.2% of the consumption group, representing an approximately 81% relative reduction.[19]

The effect was observed among initially skin-test-negative infants and those with mild skin-test positivity. The trial established that the increased peanut-allergy risk associated with severe AD can be modified through timely oral exposure.[19]

LEAP did not evaluate unrestricted home introduction in every child with severe eczema. Participants underwent structured assessment, infants with very large skin-test reactions were excluded, and peanut consumption followed a defined protocol.

Clinical translation therefore requires risk-appropriate pathways. Low-risk infants can generally undergo timely routine introduction, whereas children with severe eczema, previous reactions, or other high-risk characteristics may require expedited testing or supervised feeding.

The Enquiring About Tolerance (EAT) trial enrolled 1,303 exclusively breastfed infants from the general population and evaluated the introduction of six allergenic foods from three months of age. In the intention-to-treat analysis, food allergy occurred in 7.1% of the standard-introduction group and 5.6% of the early-introduction group, a difference that was not statistically significant.[20]

Among participants who adhered to the protocol, food allergy occurred in 7.3% of the standard group and 2.4% of the early-introduction group. The difference between the intention-to-treat and per-protocol results emphasizes the importance of feasibility, dose, frequency, and sustained consumption.[20]

EAT expanded prevention beyond a single allergen but did not establish that all infants should begin multiple foods at three months. Developmental readiness, safe food texture, breastfeeding goals, family capacity, and national recommendations remain important.

The trial supports avoiding unnecessary delay rather than forcing food introduction before an infant can safely consume complementary foods.

The Prevention of Egg Allergy with Tiny Amount Intake trial evaluated infants with eczema using a two-stage heated-egg regimen combined with intensive eczema treatment. Egg allergy developed in 38% of the placebo group and 8% of the egg-introduction group, corresponding to an RR of 0.221.[21]

The trial was stopped early because of benefit, and the high event rate in the control group reflects the selection of a particularly high-risk population.

The findings support gradual introduction of cooked egg rather than raw or pasteurized preparations. They also demonstrate that food-allergy prevention can be integrated with appropriate eczema treatment.

The study cannot determine whether intensive skin treatment independently contributed to the result because both groups received active eczema management. Extrapolation should preserve the preparation and gradual-introduction strategy evaluated rather than assuming that all egg preparations are equivalent.[21]

The Preventing Atopic Dermatitis and Allergies in Children trial used a factorial design involving 2,397 newborns. Food allergy at 36 months occurred in 2.3% of children receiving no intervention, 0.9% of those undergoing early food introduction, 3.0% of those receiving the skin intervention, and 1.2% of those receiving both interventions.[22]

Early food introduction produced an OR of 0.4, whereas the emollient intervention alone did not prevent food allergy. The absolute benefit was smaller than in LEAP because PreventADALL evaluated a general population with a lower baseline risk.[22]

The skin-intervention result is clinically important. Routine emollient application from early infancy has not consistently prevented AD or food allergy at the population level and should not be presented as a proven method of interrupting the atopic march.

Emollients and anti-inflammatory treatment remain essential for controlling established AD, reducing pruritus, improving sleep, and restoring quality of life. Therapeutic benefits for the skin are not equivalent to demonstrated prevention of future food allergy or asthma.

The LEAP-Trio investigation followed original LEAP participants into adolescence. Peanut allergy was present in 15.4% of the original avoidance group and 4.4% of the original consumption group at an average age of approximately 13 years, corresponding to an RR of 0.29.[23]

Protection persisted despite variable peanut intake after the randomized intervention ended. These findings support a durable immunological effect of early oral introduction.[23]

Long-term protection strengthens the rationale for early prevention among infants identified as high risk because of severe eczema or egg allergy. It also illustrates the appropriate use of prediction: AD identifies a population with modifiable risk, and the response should be controlled induction of oral tolerance rather than prolonged avoidance.

Whether early allergen introduction modifies subsequent asthma incidence remains uncertain and should not be inferred from the demonstrated reduction in food allergy.

Table 2

Randomized prevention trials relevant to infants with atopic dermatitis or increased allergic risk

Trial	Population and intervention	Principal result	Clinical interpretation
LEAP, 2015[19]	640 infants with severe eczema, egg allergy, or both; peanut consumption versus avoidance	Peanut allergy at five years: 3.2% versus 17.2%; relative reduction approximately 81%	Early peanut introduction substantially modifies risk in appropriately assessed high-risk infants
EAT, 2016[20]	1,303 breastfed infants; six allergenic foods from three months versus standard introduction	Intention-to-treat: 5.6% versus 7.1%; per protocol: 2.4% versus 7.3%	Potential efficacy was limited by substantial adherence challenges
PETIT, 2017[21]	147 infants with eczema; gradual heated egg and eczema treatment versus placebo	Egg allergy: 8% versus 38%; RR 0.221 (95% CI 0.090–0.543)	Structured introduction of cooked egg can reduce allergy in high-risk infants
PreventADALL, 2022[22]	2,397 newborns; early foods, emollients, both interventions, or neither	Food allergy: 0.9% with food intervention, 1.2% with both, 2.3% with neither, and 3.0% with skin intervention alone	Early foods reduced general-population risk; emollients alone did not prevent food allergy
LEAP-Trio, 2024[23]	508 original LEAP participants evaluated at approximately 13 years	Peanut allergy: 4.4% in original consumption group versus 15.4% in avoidance group	Protection resulting from early peanut introduction persisted into adolescence

Source: Prepared by the authors.

5.12 WHAT ATOPIC DERMATITIS CAN AND CANNOT PREDICT

AD predicts food allergy more strongly than asthma during the earliest years because skin disease and food sensitization overlap with the developmental period of oral tolerance.

Prediction is strongest for early moderate-to-severe or persistent disease and weaker for mild, late-onset, or transient AD. A positive food-specific immunoglobulin E result should not replace clinical history or oral challenge because AD increases the frequency of sensitization and false-positive testing.

Asthma prediction requires longitudinal observation. Recurrent wheezing during preschool years includes viral and transient phenotypes. A child should not be considered to have persistent asthma solely because AD is present.

Respiratory risk becomes more compelling when AD is persistent, objective sensitization is present, clinical food allergy coexists, wheezing occurs outside acute infections, or symptoms continue into school age.

The traditional atopic march remains useful as a simplified educational model only when its limitations are clearly stated. It describes one common trajectory but not an obligatory progression.

Atopic diseases may develop in different sequences, coexist, remit, or remain isolated because shared genetic and epithelial mechanisms produce branching rather than linear outcomes.

Prediction does not demonstrate that treatment mediates the relationship. Effective topical therapy improves pruritus, sleep, secondary-infection risk, quality of life, and cutaneous inflammation and should be initiated promptly.

Current evidence does not prove that topical corticosteroids, calcineurin inhibitors, biologic therapy, or other treatments for established AD prevent subsequent asthma, even if early control could theoretically reduce cutaneous sensitization.

5.13 CLINICAL FRAMEWORK

The clinical objective is to convert a heterogeneous association into proportionate action.

Table 3

Risk-stratified interpretation and management

Clinical pattern	Risk interpretation	Appropriate action	What should be avoided
Mild, transient, well-controlled AD without a reaction history	Risk is higher than in children without AD but generally remains modest; progression is not inevitable	Optimize routine skin care, introduce age-appropriate allergenic foods without unnecessary delay, and maintain usual respiratory follow-up	Broad immunoglobulin E panels, prophylactic elimination diets, and deterministic counseling
AD beginning during the first months and requiring prescription anti-inflammatory treatment	Increased food-allergy risk while the oral-tolerance window remains open	Review feeding and reaction history promptly and plan peanut and cooked-egg introduction according to risk-based guidance	Prolonged avoidance while awaiting nonspecific testing or relying on emollients alone for prevention
Persistent moderate-to-severe AD despite optimized treatment	Increased probability of sensitization, food allergy, and later asthma	Confirm diagnosis and adherence, intensify treatment, obtain a focused food history, and consider dermatology or allergy referral	Assuming that foods cause every exacerbation or eliminating several foods without evidence
Immediate symptoms following a specific food	Clinical food allergy is possible; eczema alone neither proves nor excludes it	Obtain a reaction-focused history, test only the suspected food when indicated, establish an emergency plan, and consider supervised challenge	Home re-exposure after a severe reaction or diagnosis based solely on sensitization
AD accompanied by confirmed food allergy or multisensitization	High-risk phenotype for school-age wheezing and asthma, particularly when AD persists	Ask longitudinally about nocturnal cough, exercise symptoms, recurrent wheezing, and bronchodilator response	Preemptive asthma diagnosis or controller medication without respiratory indications
Recurrent preschool wheezing	AD and sensitization increase the probability of persistent asthma, but transient viral wheezing remains possible	Characterize triggers and interval symptoms, perform lung-function testing when age appropriate, and treat according to asthma recommendations	Classifying every wheezing episode as asthma exclusively because eczema preceded it

Source: Prepared by the authors.

5.14 CERTAINTY OF EVIDENCE AND RESEARCH PRIORITIES

The certainty that infant AD is associated with subsequent clinical food allergy is moderate to high at the population level. Temporality, biological plausibility, challenge-confirmed cohorts, phenotype gradients, and a large meta-analysis provide convergent evidence.

Individual predictive certainty is lower because the prevalence of food allergy, AD definitions, patterns of dietary exposure, ancestry, and access to diagnostic oral challenge vary among settings.

The certainty that AD is associated with subsequent asthma is moderate. The overall association is consistent, and persistence, severity, sensitization, and coexisting food allergy demonstrate coherent risk gradients.

Causal certainty is lower because shared genetic and epithelial susceptibility, respiratory infections, tobacco exposure, family history, and diagnostic surveillance can produce similar patterns.

Evidence that early oral allergen introduction prevents specific food allergies is strong for peanut among high-risk infants. Evidence is also supportive for appropriately prepared egg and broader allergen introduction when adherence is achieved.

These results do not establish asthma prevention. Evidence that emollient-only primary prevention or conventional treatment of established AD prevents food allergy or asthma remains insufficient.

Future cohorts should use repeated objective assessments of AD severity, transepidermal water loss, standardized sensitization measures, oral food challenges, school-age asthma definitions, lung-function testing, environmental exposures, genotype, and serial microbiome measurements.

Prediction models require external validation, calibration, decision-curve analysis, and evidence that their clinical use improves outcomes rather than merely classifying children into risk categories.

Intervention studies should evaluate integrated pathways in which early severe AD prompts optimized anti-inflammatory treatment, nutritional assessment, and timely supervised allergen introduction.

Randomizing children to inadequate skin treatment would be unethical. Pragmatic trials could compare treatment timing, treatment intensity, and models of coordinated allergy prevention while maintaining accepted eczema care in all groups.

6 LIMITATIONS

This article is a structured narrative review rather than a prospectively registered systematic review with duplicate screening, a formal PRISMA flow diagram, and study-level risk-of-bias assessment. Publication and selection bias remain possible.

Definitions varied considerably. AD was established through parental report, medical examination, physician diagnosis, or administrative coding. Food-allergy outcomes ranged from oral-food-challenge confirmation to healthcare utilization, while asthma definitions ranged from preschool respiratory symptoms to school-age physician diagnosis.

Trajectory analyses depend on assessment timing, missing observations, treatment exposure, and statistical classification. Similar phenotype labels across cohorts do not necessarily represent identical clinical populations.

Administrative databases provide large samples and estimates of absolute burden but are especially vulnerable to diagnostic misclassification, healthcare-utilization bias, and incomplete recording of disease severity or family history.

Most prognostic evidence is observational. Shared genetic susceptibility, socioeconomic characteristics, feeding practices, environmental smoke, infections, and healthcare utilization may confound the associations.

Sensitization may function as a mediator, effect modifier, or common marker of susceptibility. Statistical adjustment for sensitization can therefore change the causal question being answered.

Prevention trials primarily evaluated food allergy rather than asthma and enrolled populations with different baseline risks. LEAP and PETIT cannot be generalized directly to every infant, whereas general-population trials have lower event rates and substantial adherence challenges.

No included randomized trial proves that controlling established AD alone prevents future respiratory disease.

Several reported estimates were relative measures. Large ORs do not equal individual probabilities, and ORs may overstate risk ratios when outcomes are common.

Clinical counseling should combine phenotype-specific relative evidence with local baseline risk, absolute event rates, and the certainty of the diagnosis.

7 CONCLUSION

Atopic dermatitis is an informative predictor of childhood food allergy and asthma, but it is not the obligatory first stage of an inevitable atopic march. The most important prognostic gradient is produced by very early onset, persistence, greater severity, objective allergic sensitization, and coexisting clinical food allergy.

Prediction is strongest and most immediate for food allergy. Infants with early treatment-requiring or moderate-to-severe AD have a substantially increased probability of peanut and egg allergy. Sensitization alone is common, however, and must not be confused with clinical disease. Focused history, targeted testing, and oral food challenge when indicated are preferable to broad screening panels.

Asthma risk is concentrated among persistent and sensitized AD phenotypes and is amplified when food allergy coexists. Mild, transient, and nonsensitized eczema has substantially less prognostic importance. Respiratory surveillance should therefore be proportionate and symptom-driven and should distinguish recurrent preschool viral wheezing from persistent school-age asthma.

AD should prompt prevention rather than reflexive food avoidance. Timely introduction of peanut and appropriately prepared egg can materially reduce food allergy among selected high-risk infants. Emollient-only primary prevention has not reliably prevented downstream allergic disease. Established AD must nevertheless be treated actively to protect the skin, sleep, and quality of life, without promising that conventional treatment will prevent asthma.

The most defensible clinical model is individualized and dynamic. Age at onset, severity, persistence, sensitization, food reactions, and family history should be documented, and risk should be reassessed as the phenotype evolves. Dermatological, nutritional, and allergy care should be coordinated when risk is high. Future validated prediction models and integrated intervention trials may refine this strategy without reintroducing rigid assumptions about a universal atopic march.

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