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# Timing of complementary feeding: Introduction and the risk of atopic dermatitis in infants: A review of the literature

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## ABSTRACT

Atopic dermatitis (AD) is a long-term inflammatory disease with many causes. It manifests itself with typical eczematous lesions and severe itching. Genetically or immunologically determined skin barrier dysfunction plays an important role in the pathological picture, contributing to the chronic nature of this disease. AD, one of the most common dermatoses in the pediatric population, is usually the primary manifestation of the so-called "atopic march." This phenomenon predisposes patients to the development of subsequent allergic diseases, including bronchial asthma and allergic rhinitis. Genetic and environmental aspects, as well as immunological dysfunction, interact in a complex cascade to drive the pathomechanism of the disease. The understanding of how diet - specifically when babies start solids -impacts the development of Atopic Dermatitis (AD) has undergone a significant shift. The standard view was to consider that the answer lies in avoiding allergens and delaying their introduction, but the 'dual-allergen exposure hypothesis' challenges that old belief. Instead, it suggests that early contact through the diet is the mechanism that teaches the body to tolerate these foods. This review examines the latest evidence to pinpoint the optimal window for complementary feeding to prevent AD before it starts.

**Keywords:** atopic dermatitis, infants, complementary feeding, solid foods introduction, primary prevention, food allergy.

## 1. INTRODUCTION

Commonly known as eczema, atopic dermatitis is a chronic inflammatory skin condition characterized by recurring symptoms and represents a significant public health burden among children worldwide. Current data suggest that AD affects up to 20% of children in developed countries (Nutten, 2015), serving not only as a source of reduced quality of life but also as the first symptom in the "atopic march" - progression, which frequently leads to the subsequent development of IgE-mediated food allergies, allergic rhinitis and asthma (Bantz et al., 2014).

The rise in the incidence of these diseases underscores the need to detect modifiable risk factors and implement effective prevention strategies. An essential part of these analyses is the assessment of nutritional strategies that aim to reduce the risk of developing allergies by early exposure to complementary foods.

Until the start of the 21st century, clinical protocols for expanding infants' diets mostly relied on the idea of avoiding antigens to prevent sensitization (Halcken et al., 2021). In line with this, the medical consensus at the time recommended delaying the introduction of high-allergen foods (especially peanuts, eggs, and fish) until after the child's first birthday (Greer et al., 2019).

Such an approach rested on the assumption that the immature infant's immune system required protection from antigenic load to prevent sensitization (Halcken et al., 2021; Ierodiakonou et al., 2016). Data from longitudinal studies have shown that the elimination strategy did not reduce the incidence of atopic diseases and, in certain groups, may paradoxically have increased the risk (Fleischer et al., 2021). Consequently, major health organizations revised dietary guidelines over the last decade in favor of the "dual-allergen exposure hypothesis." According to the hypothesis, the interaction of the damaged epidermal barrier with antigens characteristic of AD triggers a cascade of sensitization processes. Simultaneously, early oral intake supports the development of specific immune tolerance, as stimulation of gut-associated lymphoid tissue (GALT) influences this process (Bantz et al., 2014).

Current high-quality scientific evidence, including systematic reviews and groundbreaking randomized controlled trials (RCTs), confirms the validity of revising existing paradigms. Early introduction of specific antigens into the infant diet may help protect against the development of allergic diseases. The current EAAACI position statement from 2020 advocates for early exposure to peanuts and eggs (in cooked form) as a key part of a prevention strategy. The RCT studies, including the groundbreaking LEAP study, show that the period from the 4th to the 6th month of life is decisive in the development of immune tolerance. Evidence demonstrates that early allergen exposure during this stage significantly reduces the risk of sensitization and the development of full-blown allergic diseases later in life. Moreover, the Enquiring About Tolerance (EAT) study, an ambitious RCT evaluating the early introduction of six allergenic foods in breastfed infants, demonstrated that adhering to an early introduction protocol resulted in a lower number of peanut and egg allergy in the per-protocol analysis (Halcken et al., 2021).

Despite well-established evidence of the preventive effectiveness of early antigen stimulation in IgE-mediated diseases, the overall impact of the dietary expansion schedule on general health parameters remains unclear. It remains an open question how the sequence and timing of introducing other complementary foods influence the risk of different disease entities. In particular, the interaction between introducing regular foods (including non-allergenic grains, fruits, and vegetables) and the course of broader atopic phenotypes - namely, eczema and wheezing - requires rigorous investigation. Introducing large amounts of solid foods too early can damage the developing intestinal lining, triggering nonspecific inflammatory responses. On the other hand, delaying dietary diversification beyond 6 months may negatively influence the development of immunological resilience (Fewtrell et al., 2017). The observational evidence varies. Some studies indicate that early exposure before 4 months does not offer protective effects in the development of food hypersensitivity (Burgess et al., 2019).

Additionally, in certain groups, the introduction of solids at age  $\geq 4$  months, rather than  $< 4$  months, has been linked to increased food sensitization (Koplin et al., 2010; Roduit et al., 2014). An essential challenge in interpreting the cited observational data is the problem of reverse causality. Parents of infants with early eczema symptoms may intentionally delay dietary diversification, distorting the correlation between the timing of food introduction and the severity of the condition. The latest cohort study attempted to eliminate these errors by analyzing the impact of the timing of solid food introduction within the recommended range of 4 to 6 months of age. The results indicate that introducing cereal products (by which we mean porridge in the context of the Study) at four months rather than six months is linked with a bigger risk of eczema in specific pediatric subpopulations. These findings support current recommendations to introduce solid foods closer to 6 months of age (provided, of course, the infant is ready) (D'Hollander et al., 2023).

The conflict between the need to introduce specific allergens (peanuts/eggs) early to build tolerance and the potential risks of introducing general solids too early creates a clinical dilemma. Given the nuances between targeted allergen introduction and the general timing of complementary feeding, and the critical need to clarify preventive strategies for common atopic diseases, this paper aims to review the available literature concerning the timing of introducing complementary feeding and its potential influence on the risk of atopic dermatitis in infants. This review will synthesize findings from meta-analyses of cohort studies, RCTs, and specific longitudinal studies to provide a comprehensive view of the current evidence base, distinguishing between the prevention of specific food allergies and that of cutaneous atopy.

## 2. REVIEW METHODS

This paper provides a comprehensive review of the literature on the association between age at introduction of complementary solid foods and the risk of developing atopic dermatitis (AD) or eczema in infants and young children.

We systematically searched electronic medical databases using relevant medical subject headings (MeSH terms) and keywords. Keywords included: "Timing of introduction to solid food", "Age at introduction to complementary solid food", "complementary feeding", "Atopic dermatitis", and "eczema".

The electronic databases searched included PubMed and EMBASE, supplemented by searches in other scientific platforms such as ScienceDirect, Springer, and Google Scholar.

The review encompassed a variety of high-quality Study designs to synthesize the evidence base. Included articles were clinical research, systematic reviews, meta-analyses, randomized controlled trials (RCTs), cohort studies, and observational studies.

Two authors selected the papers based on predefined inclusion criteria. Criteria for inclusion focused on studies investigating the association between the timing of introducing complementary solids (excluding milk products) or specific allergenic foods (such as egg or peanut) and the occurrence of atopic dermatitis or eczema. The authors eliminated the publications written in languages other than English. Furthermore, they excluded studies concentrating exclusively on outcomes unrelated to AD. The PRISMA flow diagram (Figure 1) details the selection process for the included articles.

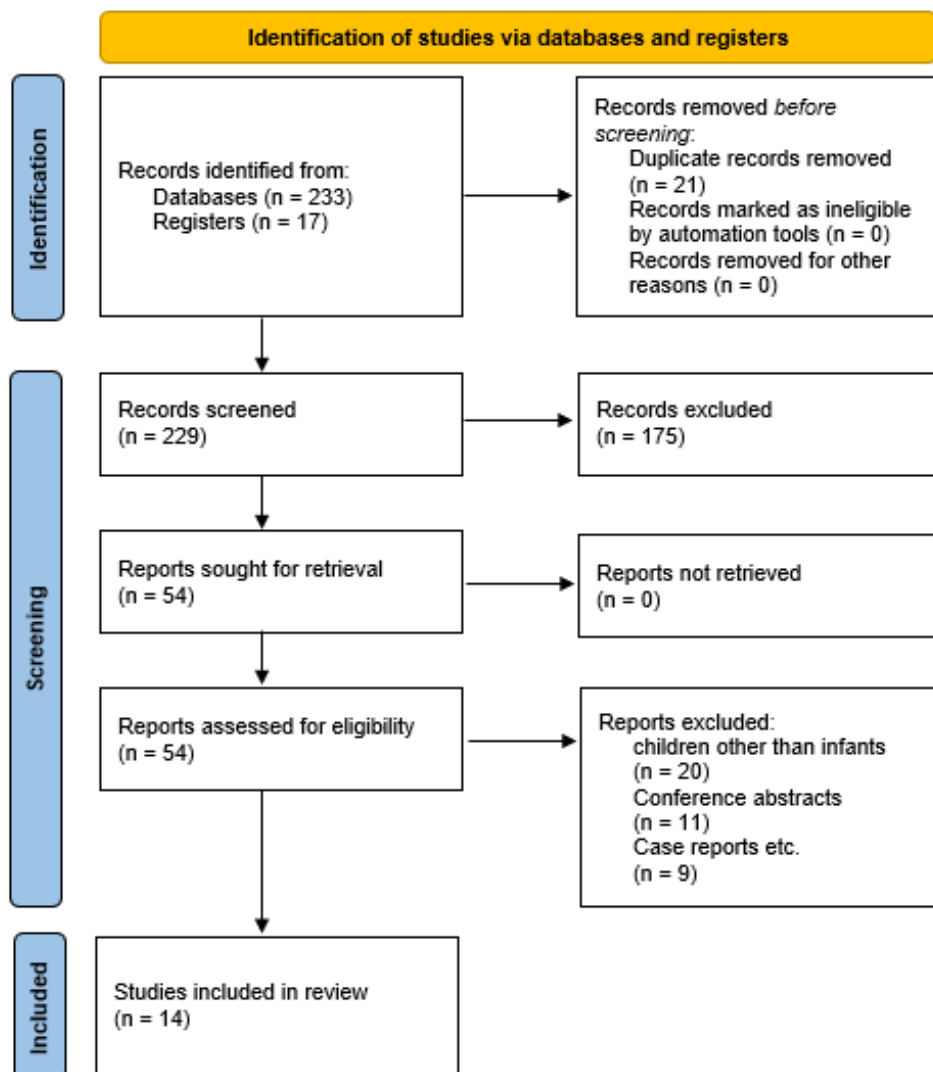


Figure 1. PRISMA chart

### 3. RESULTS AND DISCUSSION

Research on when to introduce solid foods has delivered significant, though sometimes inconsistent, conclusions. This shifting landscape has required a major overhaul of practice guidelines to prevent eczema and IgE-mediated allergies.

A synthesis of high-level evidence - including both epidemiological observations and intervention studies codified in meta-analyses - highlights a fundamental divergence in dietary management. In particular, this data clearly distinguishes the chronological initiation of general complementary feeding from the targeted, proactive administration of high-potency allergens (Fleischer et al., 2021). Evidence from interventional studies, particularly randomized controlled trials, confirms the effectiveness of early, intentional exposure to high-risk food allergens (LEAP; EAT). Research into the optimal timing for introducing foods into the diet has clarified one essential point: there is a specific "window of opportunity" period in early infancy. Exposing infants to allergens during this short period is associated with a significant reduction in the prevalence of clinical allergy. Additionally, this preventive strategy reduces the incidence of immune sensitization to these food proteins. In particular, the studies indicate that introducing well-cooked eggs during the defined early window of complementary feeding is associated with a lower risk of egg allergy. Similarly, the well-timed incorporation of protein from peanuts into the infant diet, when compared with delayed introduction, was associated with a reduction in the development of peanut allergy (Muraro et al., 2022).

These impressive results from interventional studies highlight a significant discrepancy with existing clinical knowledge, which has traditionally recommended avoiding allergens. In line with this updated knowledge, the European Academy of Allergy and Clinical Immunology (EAACI) Task Force has made specific recommendations for introducing these allergens. - recommending the optimal window for initiating exposure to both well-cooked egg and age-appropriate peanut preparations, which falls within the initial months of complementary feeding. However, the EAACI guidelines also warn that some preparations, such as raw or uncooked pasteurized eggs, should be avoided when introducing them. In addition, guidelines for introducing peanuts into the diet explicitly tailor peanut introduction strategies for populations with a high prevalence of peanut allergy (Muraro et al., 2022; Halcken et al., 2021).

The investigation into the early introduction of multiple allergenic foods at once introduces even more complexity. A novel randomized controlled trial examined the systematic introduction of a panel of six common allergenic foods to infants who were exclusively breastfed. It compared such intervention with the conventional feeding practice common in the United Kingdom, which typically delays the introduction of solid foods to around the conventional later threshold of six months of age (Halcken et al., 2021). Although the preliminary analysis, assessing results solely based on assignment to the intervention group (intention-to-treat approach), did not show apparent overall effectiveness in reducing allergies across the entire panel of six foods included in the intervention, a subsequent analysis focusing only on participants who strictly adhered to the recommended early feeding protocol (per-protocol analysis) showed convincing preventive benefits. This strictly conducted Study, in accordance with the protocol, showed a significantly lower incidence of general food allergies in the group with early food introduction compared to the group with standard food introduction. This protective effect peaked for both peanut and egg allergies in this high-adherence group.

Such results raise a key clinical question on the dose dependency. They suggest that the protective immunological effect relies on maintaining minimum weekly thresholds for allergenic protein intake, as stated in the protocol followed by the high-adherence group (Halcken et al., 2021).

Unfortunately, implementing a general early introduction protocol involving multiple allergens proved challenging to implement universally among caregivers, despite its safety (Chan et al., 2024).

In contrast to clear interventional data on specific allergens, observational studies offer a less certain perspective on introducing complementary solids. An analysis of collective data from numerous observational cohort studies has not provided clear evidence that introducing solid foods at a very early age - specifically before 4 months - protects against the development of general food allergies. In fact, observational data suggest that introducing general complementary solids after that specific early age threshold is linked to an increased likelihood of food sensitization (Burgess et al., 2019). These data indicate the existence of a transient "window of opportunity" for inducing oral tolerance - a physiological opening that becomes virtually inaccessible as a result of excessive delay in introducing solid foods into the diet. Importantly, prolonged withholding of solid foods did not confer any compensatory preventive benefits in preventing the development of overt allergic phenotypes (Muraro et al., 2022).

Research also focused on outcomes beyond IgE-mediated food allergy, particularly the prevention of eczema. Longitudinal cohort studies on that topic reveal important modifying factors related to the timing of the very first solid food introduced (D'Hollander et al., 2023).

The association between the age of introducing typical infant cereal and the probability of developing eczema is also a subject for investigation, yielding interesting results. According to the investigation, initiating such feeding at an earlier age, relative to a later-established threshold of six months, can be associated with a higher probability of the disease. What is important is that this unfavorable association was observed primarily in a subgroup of infants: those without asthma in their family and who were not breastfed by their mothers during the introduction of solid foods. This discovery demonstrates that the link between complementary feeding and eczema is not universal. Instead, genetic predisposition and breastfeeding status play an important role in defining this risk. A similar pattern of effect modification appears when assessing wheezing in later childhood. All in all, these findings reinforce the established Recommendation to wait until approximately six months of age to introduce solid foods (D'Hollander et al., 2023). Table 1 shows a summary of evidence associating the timing of complementary feeding with atopic disease.

**Table 1.** Summary of evidence associating the timing of complementary feeding with atopic disease.

Timing of Introduction	Food Type	Outcome Measure
From 4 months	Egg	Egg Allergy
From 4 months	Peanut	Peanut Allergy
< 4 months	General Solids	Food Sensitization
4 vs 6 months	General Solids	Food Sensitization
4 vs 6 months	Infant Cereal	Atopic Dermatitis (Eczema)

All in all, the available evidence points to the need for a dual clinical strategy: early, targeted introduction of particular major allergens (such as eggs and peanuts) to reduce food allergy risk, while supporting existing guidelines for general complementary feeding at six months. Such an approach is crucial for preventing wheezing and atopic dermatitis in vulnerable groups. The complicated relationship among food type, exact timing, immune mechanisms (sensitization versus overt allergy), and patient characteristics should be taken into account when developing comprehensive prevention strategies. The uncertainty surrounding the prevention of food allergy underscores the ongoing need for extensive, multinational clinical research using rigorous diagnostic criteria to optimize these feeding guidelines. Table 2 compares dietary strategies for the prevention of specific food allergies versus those for atopic dermatitis.

**Table 2.** Comparison of dietary strategies for the prevention of specific food allergies versus atopic dermatitis.

Feature	Targeted Allergen Introduction	General Complementary Feeding
Target Foods	High-risk allergens (Peanut, Egg)	Non-specific solids (e.g., Infant Cereal, Vegetables)
Primary Goal	Induction of immune tolerance (prevention of specific allergy)	Nutritional supplementation; avoiding non-specific immune stimulation
Optimal Timing	4 to 6 months	Around 6 months
Rationale	"Window of opportunity" for tolerance induction supported by RCTs (e.g., EAT Study).	Early introduction (4 mo) is associated with higher odds of eczema and wheezing in some subgroups.
Key Recommendation	Introduce early in age-appropriate forms (e.g., peanut butter, well-cooked egg).	Delay general solids slightly closer to 6 months, especially in non-risk groups.

#### 4. CONCLUSIONS

This review confirms the complex relationship between the timing of complementary feeding and the risk of developing atopic diseases. It also highlights the need for a differentiated approach to infant nutrition. Current evidence suggests that doctors should recommend a strategy that prioritizes introducing well-cooked eggs and peanuts between 4 and 6 months of age to prevent specific

allergies. At the same time, guidelines for the general introduction of other, nonspecific complementary foods should remain cautious, favoring their introduction closer to 6 months of age to reduce the risk of broader atopic conditions such as eczema. Despite significant advances from RCTs, the best way to comprehensively prevent food allergies remains uncertain.

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### Authors' Contributions

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### Ethical approval

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### Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

### Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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