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Primary, secondary and tertiary prevention of food allergy: current practices and future directions

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Abstract

The incidence of food allergies has risen around the globe, and experts have been exploring methods of preventing such allergies in young children to ease the burden of disease and reduce the morbidity and mortality caused by anaphylaxis to food allergens. Such preventative measures can be categorised as primary, secondary and tertiary prevention, which are discussed in detail in this review. Primary prevention is defined as the prevention of becoming sensitised towards specific allergens. The evidence suggests that avoiding common allergenic foods during pregnancy and breastfeeding is not protective against food allergies, and guidelines recommend weaning from 4 to 6 months of age, with recent studies supporting the early introduction of peanuts at 4 months to prevent peanut allergy. Secondary prevention targets patients who are already sensitised and aims to halt the progression of sensitisation, with evidence for high rates of success and safety in trials of early introduction to milk and peanuts using oral immunotherapy in sensitised infants. Tertiary allergy prevention focuses on reducing the risk of a patient having anaphylaxis, with oral immunotherapy being the most common method of promoting tolerance in allergic children. Several studies have demonstrated successful reintroduction for milk, egg and peanut; however, no such guidelines are recommended for other foods. Finally, dietary advancement therapy in the form of milk and egg ladders has been employed as a method of primary, secondary and tertiary prevention of allergies, particularly in Ireland, the UK and Canada.

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Introduction

It has been more than 15 years since Allergologia et Immunopathologia presented the last literary review of allergy prevention in 2007.¹ Since then, several changes have been made, most of them focused on changes in dietary advice and guidelines. Given the importance of new evidence that has emerged in the past decade, physicians have continued to pursue pathways of allergy prevention. The prevalence of allergic diseases has increased exponentially across the world.² It has been described that 11%-28.7% of children across Europe are IgE-sensitised to at least one food product.^{3,4} Cows' milk, hens' eggs, peanuts and nuts are more prone to induce an allergic response.³ As a result, individuals with food allergies utilise more healthcare resources, leading to a rise in direct costs to the healthcare system.^{5,6}

Allergic diseases prevention is well-known and has been studied for more than 100 years, and its importance has been emphasised during the three main allergy epidemics: The 'hay fever epidemic in 1870', the epidemic of asthma from 1960 to 2000, and the rise of food allergy from 1990 to present day.⁷ Three stages of allergy prevention have been well established, each one focusing on prevention at different stages, namely primary, secondary and tertiary allergy prevention (Figure 1). The goal of primary allergy prevention is to stop the onset of IgE sensitisation to the food-specific allergen. In secondary prevention, the person has already been IgE sensitised, and the goal is to interrupt the full development of a food allergy. Finally, in tertiary prevention, food allergy has already emerged, and we seek to desensitise the individual and build tolerance towards their allergen.¹

This review aims to examine the most up-to-date research surrounding allergy prevention from the antenatal course to early childhood.

Primary Allergy Prevention

Primary allergy prevention is defined as the prevention of becoming sensitised towards specific allergens. This type

of prevention particularly targets the perinatal, neonatal and early infancy period.¹

Maternal diet during pregnancy

Complete avoidance of common culprit foods during pregnancy to avoid food allergy, once a clinical guideline in many countries, has now been debunked. It had its roots in the hypothesis that the introduction of food will increase allergen sensitivity due to gut immaturity leading to a decrease of permeability of potential allergens. This led to several changes in major allergy societies that advise a late introduction of allergenic foods independent of their allergic risk factors.^{8,9}

Nowadays, maternal diet in the antenatal period has predominantly trended towards an increase in the introduction of different foods to prevent allergic diseases in children as part of a primary prevention strategy. A diverse maternal diet during pregnancy has been implicated in influencing allergy prevention in children. In 2002, it was shown that maternal antigens of beta-lactoglobulin (BLG), ovalbumin (OVA) and the major birch pollen allergen (Bet v1) are transferred via the placenta and contribute to the normal development of immunity.¹⁰ A Cochrane review, conducted in 2012, found that eliminating common allergens from maternal diets (peanuts, dairy, egg and wheat) added no benefit in preventing allergies in their child in the first 18 months of life. It was even shown that these diet restrictions were associated with a statistically significant lower mean gestational weight gain, a non-significantly higher risk of preterm birth, and a non-significant reduction in mean birth weight. These findings suggest that consuming a varied and balanced diet during pregnancy reduces the risk of food allergy in the child compared to the previous misconception of elimination diets during pregnancy.

Recent studies have also investigated the role of maternal dietary patterns in the prevention of food allergies. A study in Singapore found that a dietary pattern of seafood and noodles during pregnancy was associated with a reduced risk of developing allergic sensitisation in 735

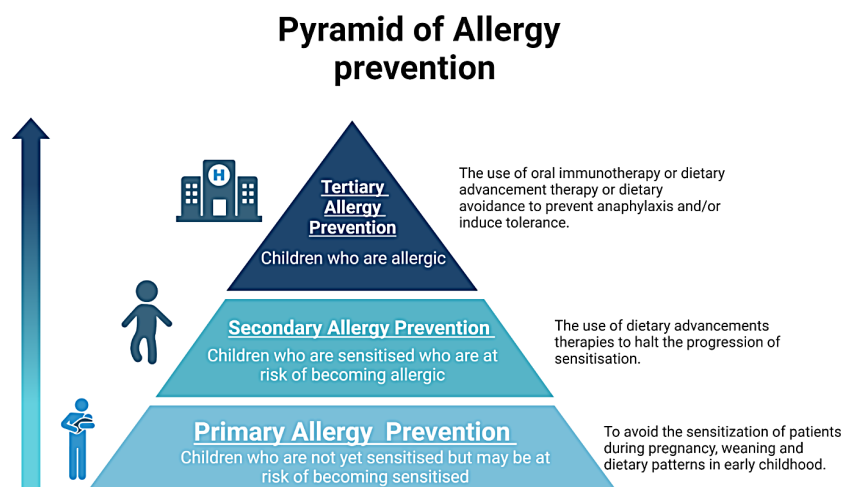


Figure 1. The three tiers of allergy prevention.

children at 18 months and 36 months of life ([odds ratio (95% confidence interval): 0.7 (0.5-0.9)] and [odds ratio (95% confidence interval) 0.7 (0.6-0.9)], respectively) compared to dietary patterns of vegetables, fruits, white rice, pasta, cheese and processed meat.¹¹ This is thought to be due to the fatty acids contained in seafood, which may play a key role in the protective effect of early immunological development towards atopy sensitisation and allergy development.¹² Another population-based cohort study in Finland among 6288 mothers found that high consumption of cow's milk products during pregnancy was associated with a lower risk of cow's milk protein allergy (CMPA) in the offspring [odds ratio (OR) 0.56, 95% confidence interval (CI) 0.37-0.86; $p < 0.01$], however, this association was only present in non-allergic mothers. Indeed only a high consumption of dairy products during pregnancy constituted a protective factor compared to dairy consumption during lactation [odds ratio (OR) 0.30, confidence interval (CI) 0.13-0.68, $p = 0.01$]. This was supported by a correlation between Cord blood IgA levels to beta-casein with the maternal consumption of milk products; $R = 0.216$, $p = 0.003$ in children who did not develop CMPA and $R = 0.206$, $p = 0.05$ in children who developed CMPA, indicating exposure to cow's milk and activation of antigen-specific immunity in the infant during pregnancy.¹³

In addition to the consumption of dairy during pregnancy, the consumption of peanuts and nuts has also been shown to prevent food allergies in the offspring. This association was found in a prospective cohort study carried out in 2014, which showed the incidence of peanut and tree nut allergy in the offspring was significantly lower among children of non-allergic mothers who consumed peanuts and tree nuts in their peri-pregnancy diet (≥ 5 times vs < 1 time per month: odds ratio = 0.31; 95% CI, 0.13-0.75; $P(\text{trend}) = 0.004$).^{14,15} This was supported by a more recent prospective cohort study in 2022, showing maternal peanut consumption during pregnancy was associated with a decreased risk of food allergy in children (AOR, 0.57; 95% CI, 0.33-0.98).¹⁶ While there is evidence to support the consumption of a healthy balanced diet during pregnancy to prevent food allergies in the offspring, further randomised control trials are required to ascertain the protective effect of the consumption of allergenic foods during pregnancy.

Breastfeeding

There is a wide array of evidence that supports the benefits of breastfeeding.^{15,16} A study in 2014 found a reduction in the incidence of CMPA with exclusive breastfeeding for 4 months compared with partially breastfeeding with cow's milk protein formula at up to 24 months of age (OR 0.2 [95% CI, 0.04-0.7])¹⁷ This could indicate that early exposure to cow's milk protein might be associated with its allergy development. However, studies exploring the relationship between the diets of breastfeeding mothers and food allergy in their infants have been non-conclusive. Except for mothers of children who already show signs of allergy, diet avoidance of highly allergenic foods in breastfeeding mothers is not recommended. Therefore, there is a lack of evidence that supports food allergen avoidance in breastfeeding mothers as a mechanism for primary

allergy prevention in their children. There is however a strong emphasis on the importance of a balanced diet in breastfeeding mothers. A healthy balanced diet is crucial for the production of nutrient-rich breast milk and proper lactation. However, even in developed countries, it has been shown that the diet of breastfeeding mothers is often inadequate.¹⁸ Therefore, in terms of allergy prevention, these studies have similar implications to those performed in pregnant women. The focus of breastfeeding mothers should be on eating a complete and balanced diet rather than avoiding certain food allergens. This would be the most effective way to promote the healthy development of their child.

Weaning: The right foods at the right time

The World Health Organization Global Strategy for Infant and Young Child Feeding recommends exclusive breastfeeding for the first 6 months of life with nutritious complementary foods introduced thereafter and continued breastfeeding up to the age of 2 years or beyond.¹⁹ Guidelines formerly stated that if a mother decides to introduce complementary foods before 6 months of age, there are some foods that should be avoided because they can cause allergies, including 'wheat-based foods...eggs, fish, shellfish, nuts (and) seeds'. However, early studies suggested that there is little evidence that avoidance of such foods reduces allergic disease, in fact, the early introduction of allergenic foods including milk, eggs and peanuts between 4 and 6 months of age may be protective against future food allergy.²⁰⁻²³

Several trials in the past decade have investigated the role of early introduction of allergenic foods during weaning in allergy prevention, the first of which is the Learning Early About Peanut allergy (LEAP) trial.^{24,25} This was a randomised control trial including 640 infants aged 4 to 11 months to establish the effects of early exposure of peanuts on peanut allergy development. Participants were divided into two cohorts based on their reaction to a peanut skin-prick test (those with no measurable reaction and those with a wheal measuring 1-4 mm). Each cohort was then divided into a consumption and non-consumption group. Participants in the consumption group were given up to 6 g of protein per week up until age 60 months. At 60 months of age, a peanut allergy was then determined by doing an oral food challenge. The results showed a significant reduction in allergy development in consumption groups versus non-consumption groups. In the negative skin-prick test cohort there was a reduction of 86%, and in the positive skin-prick test cohort there was a reduction of 72%.²⁴ These results indicate that early consumption of peanuts (before 11 months of age) leads to increased peanut allergy prevention at 60 months of age.

In the following year, Du Toit et al. Toit et al. conducted a follow-up to their LEAP study.²⁶ Their aim was to investigate whether the effects of early peanut consumption resulting in peanut allergy prevention remained after 12 months of further peanut avoidance. A total of 556 participants from the LEAP trial were enrolled in this study (282 from the peanut-avoidance group and 270 from the peanut-consumption group). At 60 months of age, the

participants abstained from consuming peanuts for a further 12 months. At 72 months of age, they were assessed again for peanut allergy using the skin-prick test. Those who were in the consumption group had a prevalence of peanut allergy that was 74% lower than those who were in the peanut-avoidance group. The results of this study indicate that in infants with a high risk of developing peanut allergy, early peanut consumption (before 11 months of age) leads to a reduction in peanut allergy development by 5 years. It further demonstrated that after a 12-month period of peanut abstinence, the prevalence of peanut allergy by 6 years of age was not increased.

In 2016 Perkins et al. conducted a study to evaluate the effect of timing with respect to the introduction of allergenic food in breastfed infants.²⁷ Participants were divided into an early introduction group (3 months) and participants in the standard introduction group (6 months). They were introduced to six allergenic foods (peanuts, cooked eggs, cow's milk, sesame, whitefish and wheat) and evaluated between 1 and 3 years of age for the development of a food allergy. The study found that early introduction of allergenic food was safe and that there were no adverse effects on breastfeeding or growth.²⁷ However, it failed to show any benefit in comparison to standard allergen introduction.

Roberts et al. have performed a patient-level meta-analysis based on data from both LEAP and EAT studies to determine the effect of early peanut consumption.^{28,29} While both studies support the early introduction of allergenic foods, LEAP only included high-risk participants while EAT included participants with varying levels of risk. The intention-to-treat (ITT) analysis found a 75% reduction ($p < 0.0001$) in peanut allergy among those who consume peanuts from early infancy and the protective effects are demonstrated across all eczema severity groups, ethnicities and prior sensitisation to peanuts.²⁹ This is the first time early peanut consumption has proved to be a successful strategy to reduce peanut allergy in the general population.³⁰

The influence of diet in the early years

In 2014 Grimshaw et al. conducted a study investigating the relationship between food allergy and the pattern of food consumption rather than focusing on individual nutrients.²⁹ This hypothesis-generating study evaluated the prevalence of food allergy in children who were raised following a healthy infant diet. The study found that children were less likely to have a food allergy by the age of 2 years if they had a dietary pattern in infancy consisting of fruits, vegetables and home-cooked meals. The process by which this pattern of eating could prevent food allergy is related to the immunomodulator effects of the nutrients in these foods (vitamin C, beta carotenes, folate and oligosaccharide).³⁰

In 2019, Venter et al. investigated different measures of food diversity in the first year of life and its association with the development of food allergy over the first decade of life.³¹ Specific feeding data were collected from 969 participants at 3 months, 6 months and 12 months of age. Diet diversity was then calculated according to four

different measures - a sum of the number of food groups consumed (DD), the number of foods introduced at each time point (FD), the number of fruits and vegetables consumed (FVD), and the number of common allergens (FAD) consumed. The allergens included were milk, egg, wheat, fish, soy, peanut, tree nuts and sesame. Food allergy outcomes were then determined at ages 1, 2, 3 and 10 years. All measures of food diversity showed a consistent reduction in food allergy outcomes. Most importantly, the study found that for each additional allergenic food consumed by 1 year, the odds of developing a food allergy are reduced by 33.2% over the first decade of life.³¹

The findings of this study are multi-fold. Primarily it introduces a feasible form of primary allergy prevention. It promotes a healthy, well-rounded diet in newborns and young children. Finally, it encourages parents to feed their children the food they make at home rather than encourage the purchase of store-bought processed meals.³¹

Timing of allergenic food introduction

In 2023, a systematic review and meta-analysis focussing on the introduction timing of multiple allergenic foods (milk, eggs, fish, shellfish, tree nuts, wheat, peanuts and soya) and their association with allergy prevention was conducted.³² In the 23 trials included, multiple allergenic foods were introduced in the first year of life, and allergy development was assessed at 3-5 years.³² It was found that earlier introduction of multiple allergenic foods was associated with reduced IgE-mediated allergy to any food. Findings are consistent with the Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL) which supports the early introduction of multiple food allergens for primary allergy prevention.³³ Compared to the results of the LEAP trial which proved to be beneficial in preventing peanut allergy alone, preventing allergies to multiple foods would be of greater value to the participants and their families.^{24,33} Safety data found that earlier introduction of allergenic food was associated with higher rates of withdrawal from the intervention. In the two large multiple allergenic food trials included in the systematic review, only 29% and 34% of the participants in the early introduction groups were fully adherent to the intervention protocol.^{35,36} In another trial, intervention non-adherence was due to feeding difficulties.³⁷ In three smaller studies, greater success in introducing multiple allergenic foods was associated with the use of food protein powders rather than the stepwise introduction of whole foods.³⁸⁻⁴¹ One trial reported that early food introduction did not have any adverse effect on breastfeeding rates,³⁹ while another study reported no detectable adverse effects on infant growth, gastrointestinal health, respiratory health or development.^{40,41}

Current European Guidelines for Allergy Prevention

In 2020, the European Academy of Allergy and Clinical Immunology (EAACI) conducted a systematic review with the goal of updating their original 2014 guidelines for preventing food allergy.⁴² They looked at randomised control

trials from 1946 to 2019 including infants, children and adults at general risk and increased risk (those with atopic heredity, eczema and/or IgE sensitisation) of developing food allergy. From the studies that were reviewed, the following findings could be implicated for clinicians and families to help prevent food allergy: Introducing small amounts of cooked, unpasteurised hen's eggs into the infant diet as part of complementary feeding has shown to reduce the risk of egg allergy development in infancy. Introducing peanuts into the diet in infants aged 4-11 months was shown to reduce peanut allergy development. This intervention was most promising in infants at increased risk, and in countries with high prevalence of peanut allergy, and was shown to be more effective compared to abstaining from peanuts until children reach 5 years. The EAACI reviewed several interventions that were tested but showed to have little to no effect on food allergy development. Interventions for pregnant and breastfeeding women included: avoiding food allergens; vitamin D supplementation; fish oil supplementation; and probiotics. Interventions for infants included: hydrolysed formulas; dietary avoidance of food allergens; early introduction of food allergens; probiotics; prebiotics; synbiotics; fish oil; vitamin supplements; emollients; and environmental changes. This systematic review had several limitations. Several studies did not use appropriate criteria for food allergy diagnosis, studies were frequently small and therefore not powerful enough to detect significant differences between groups.⁴³

Changes in weaning and breastfeeding recommendations

There has been a multitude of infant feeding approaches that have been implemented throughout the years for allergy prevention. The majority focus on the timing of weaning and avoidance of potential allergens. Recommendations vary between countries which further confuses paediatricians and the public (Table 1).

A graphic representing the methods of primary prevention of food allergies is shown in Figure 2.

Secondary Allergy Prevention

Secondary prevention targets patients who are already sensitised and aims to halt the progression of sensitisation. Multiple modes of dietary advancements have been introduced, such as the introduction of baked products, food ladders and oral immunotherapy.

Early introduction using oral immunotherapy

As discussed in primary prevention, experts no longer advocate for the avoidance of 'allergenic foods', both in utero or the post-natal period, with the premise of reducing the possibility of sensitisation in the future. Early introduction of food is the mainstay of reducing sensitisation and subsequently, an allergic reaction. The first to publish this management was Reche et al. who conducted a case-control study in 2011 where 20 patients with CMPA were divided

into either strict avoidance or introduction of oral immunotherapy. All children in the case group were tolerant to milk at the age of 1 year while only three were tolerant in the control group.^{52,53} The mean age of the participants was 3 months old. This study laid the foundation for larger studies including Calvo et al. in 2020 who performed a retrospective review of 335 infants under 1 year with CMPA and introduced an up-titrating dose of cow's milk formula to 150-200 mL. More than 98% became tolerant to milk and the remaining 1.8% were able to remain asymptomatic to a certain dose of milk or its derivatives.⁵⁴ Both studies suggest that introducing milk at an early age may induce tolerance in those who are sensitised to an allergen and may not acquire tolerance naturally as they grow.

In 2017, Vickery et al. also found positive results with this approach in those with peanut allergies.⁵⁵ They hypothesised that targeting newly diagnosed young peanut-allergic children between the ages of 9 to 36 months with oral immunotherapy would produce clinical effectiveness. Children who were peanut-sensitised were also included and refer to those as having no prior history of IgE-mediated allergic reaction to peanuts but with a serum peanut -IgE > 5 kUA/L. Of the 40 children recruited to the study, nine were proven to be sensitised, but not allergic to peanuts. Participants underwent an initial-day escalation phase, followed by a build-up phase with a target maintenance dose of 3000 mg/day of peanut protein. The assessment of clinical desensitisation was a double-blind placebo-controlled food challenge of a cumulative dose of 5 g of peanut protein. Of the 32 participants who completed the treatment protocol, 30 participants had no reaction and were declared peanut desensitised. Unfortunately, the nine peanut-sensitised participants and the 31 peanut-allergic participants were all grouped into one cohort. The results of the study, although promising for oral immunotherapy as a role for inducing peanut protein tolerance, did not specify how the peanut sensitised participants performed in relation to the peanut-allergic participants.

In 2019, Berti et al. enrolled 73 infants under the age of 1 with a clinical history of IgE CMPA with a positive skin prick test to undergo a home oral immunotherapy protocol.⁵³ Upon completion of the protocol, 97% of the infants remained asymptomatic on 150 mL of cow's milk. It had a high rate of family compliance and proved that home oral immunotherapies can be carried out safely at home. It also showed that early immunotherapy helps anticipate the disease course, and for infants who are less sensitised, going through the protocol may provide an earlier unrestricted diet and can be curative. For those who are sensitised and may develop persistent CMA, an early introduction can increase the amount of milk tolerable to remain asymptomatic and reduces the risk of life-threatening allergic reaction.

Vitamin D supplementation

Recent studies showed that food allergy-related paediatric admissions and adrenaline autoinjector prescriptions are high in countries further from the equator. In 2013, Allen et al. found that infants born in Australia to parents with vitamin D deficiency (serum 25-hydroxyvitamin

Table 1. Current guidelines for breastfeeding and complementary food introduction.

Guidelines on timing of exclusive breastfeeding and introduction of complementary foods		
	Exclusive breastfeeding	Complementary feeding
World Health Organisation (WHO, 2003) ⁴²	Initiate in the first hour of birth and exclusively breastfeed for 6 months of life	Introduce at 6 months of life in addition to breastfeeding
European Food Safety Authority (EFSA) (2019) ⁴³		Most infants do not need complementary foods before 6 months of age as exclusive breastfeeding provides sufficient nutrients up to that age. Can introduce complementary foods depending on developmental readiness, e.g. pureed food from 3-4 months and self-fed finger foods: between 5 and 7 months of age. Allergenic foods (e.g. egg, cereals, fish, peanut) and gluten can be introduced when other complementary foods are introduced
European Academy of Allergy and Clinical Immunology (EAACI) (2020) ⁴⁴	Initiate in the first hour of birth and exclusively breastfeed for 6 months of life. Avoid supplementation with regular cow's milk in the first week of life	Introduce at 4-6 months, including peanut and well-cooked egg
Health Service Executive (HSE) (2022) ⁴⁵	Initiate at 6 months	Introduce at 6 months of life in addition to breastfeeding
British Society of Allergy and Clinical Immunology (BSACI) (2019) ⁴⁶	Initiate for the first 4-6 months of life	Introduce at approximately 6 months onwards. In children at high risk of developing food allergy, the introduction of eggs and peanuts is recommended to start at 4 months alongside other solid complementary foods
American Academy of Allergy, Asthma and Immunology (AAAAI) (2013) ⁴⁷	Initiate for the first 4-6 months. Using hypoallergenic formula is recommended for infants at increased risk of allergic disease who cannot be exclusively breastfed	At 4-6 months introduction of single ingredient solid foods. Allergenic foods such as eggs, dairy, peanuts, tree nuts, fish and shellfish should be introduced second to less allergenic foods
American Academy of Paediatrics (2022) ⁴⁸	Initiate approximately during the first 6 months of life	At 6 months onwards in most children. Foods rich in protein, iron and zinc. Peanuts should be introduced as early as 4-6 months.
European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (2017) ^{49,50}	Initiate for at least 4 months, but 6 months would be desirable	Should not be introduced before 4 months, but no later than 6 months
Dietary Guidelines for Americans, 2020-2025 (2021) ⁵¹	Exclusive breastfeeding, ideally for the first 6 months of life, with continued breastfeeding through the first year of life or longer.	Complementary foods and beverages should not be introduced before 4 months old. Introduce potentially allergenic foods within the first year of life and consider introducing peanut-containing foods between 4 and 6 months old
Australian National Health and Medical Research Council (2012) ⁵¹	Exclusive breastfeeding until 6 months	Complementary feeds around 6 months old, with continued breastfeeding of up to 1 year and above

D3 of 26-50 nmol/L) were 11 times more likely to have a peanut allergy and three times more likely to have an egg allergy.⁵⁵ Amongst infants who were allergen sensitised, those with vitamin D deficiency were six times more likely to develop a food allergy which demonstrates its role in preventing allergy development. Several genes are responsible for producing the enzyme that degrades vitamin D in the serum, and modification of these genes has shown to

have a differential effect on food sensitisation.⁵⁶ Another hypothesis is that vitamin D deficiency alters the skin barrier which allows for epicutaneous sensitisation of food allergens which predisposes the patient to IgE-mediated induced anaphylaxis. Overall, these results suggest that vitamin D sufficiency could be a protective factor in preventing the development of food allergies in sensitised children. However, more research is needed to prove

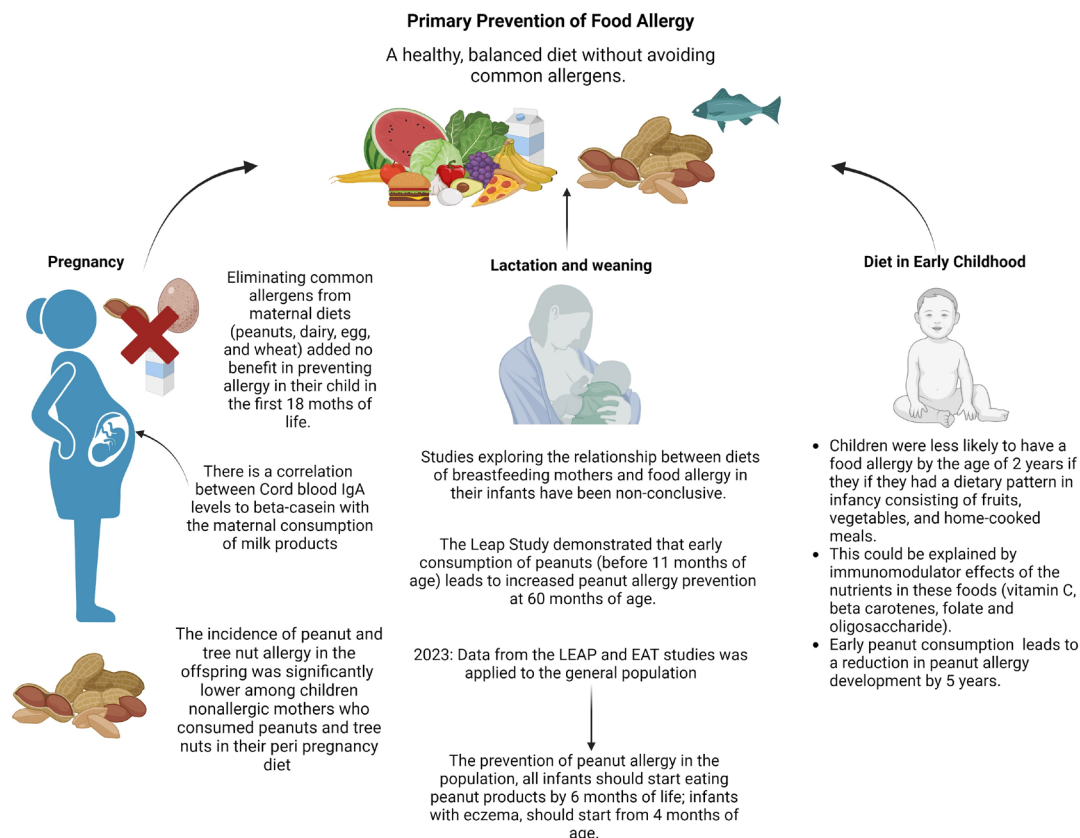


Figure 2. Summary of primary prevention of food allergy.

whether vitamin D supplementation has a role in preventing or treating food allergies.

Tertiary prevention

Tertiary allergy prevention focuses on reducing the risk of a patient having anaphylaxis and this is usually done by avoiding the food allergen and appropriate management of anaphylaxis with adrenaline autoinjector.⁵⁷ This is an approach that has decreased the mortality of allergic patients worldwide but has not been effective in reducing the prevalence of the disease.⁵⁸ While the administration of adrenaline is the mainstay of treatment of anaphylaxis, the timely recognition of the signs of anaphylaxis as well as the correct administration of the autoinjector requires thorough parent and patient education.⁵⁹ The knowledge of parents on the management of anaphylaxis has been shown to be suboptimal,^{60,61} and adolescents with allergies are at a higher risk of morbidity and mortality from anaphylaxis, partly attributed to risk-taking behaviours and the transition from parent management to self-management.⁶²

Oral immunotherapy (OIT) is now the most common way to prevent the lifelong burden of avoiding an allergen to prevent anaphylaxis for several food allergies. Oral immunotherapy is defined as administering increasing doses of a food allergen (usually in a food vehicle) to an allergic patient to increase the threshold at which they react to it.⁶¹ The general structure of OIT protocols

consists of three phases: (i) day escalation, (ii) build up, and (iii) maintenance.⁶² While the most frequent route of administration of allergen immunotherapy is the oral route where the allergen is either immediately swallowed (OIT) or held under the tongue for a while (sublingual immunotherapy, SLIT), there are current ongoing studies using the subcutaneous route (subcutaneous immunotherapy, SCIT) and epicutaneous immunotherapy (EPIT).⁶³

EAACI has summarised its guidelines and recommendations on the safety and effectiveness of immunotherapy for several allergens based on evidence from multiple trials.⁶⁴

Peanut oral immunotherapy

The current guideline from EAACI is that OIT is recommended as a treatment option to increase the threshold of reaction in children with peanut allergy from around 4-5 years of age.⁶³ This guideline is based on evidence from meta-analyses of studies,⁶⁵ including Varshney et al in 2011.⁶⁴ Participants were aged between 1 to 16 years and had a clinical history of at least one IgE-mediated reaction to peanut ingestion and a positive skin prick test to peanuts. The protocol took place for 44 weeks.⁶⁴ Participants were randomly assigned to either treatment groups or control groups. The dosing of peanut flour began at 0.1 mg of peanut protein, which was increased every 2 weeks up to a maximum of 5 g. 16 participants of the initial 19 were able to complete the treatment protocol.⁶⁴ These

16 participants were able to consume 5 g of peanut protein compared to the placebo group who were able to consume on average a maximum of 280 mg of peanut protein.⁶⁴

In 2011, Anagnostou et al. conducted a similar prospective cohort study which took place over 32 weeks and included an initial dosing of peanut protein followed by build-up doses.⁶⁵ Those who completed the treatment protocol were able to consume up to 6.6 g of peanut protein. This was a higher threshold than any previous study.⁶⁵

Similarly, 3 years later, Anagnostou et al. designed a 26-week long treatment protocol which also had the capacity of inducing desensitisation.⁶⁶ It was a double-blind placebo-controlled food challenge whereby participants aged 7 to 16 years were given progressively larger doses of peanut protein every 2 weeks up to a maintenance dose of 800 mg.⁶⁶ These participants all had at least one previous IgE-mediated reaction to peanuts and a positive skin-prick test. Upon completion of the protocol, 26 out of the 39 participants were peanut desensitised. Desensitisation was defined as no reaction to a double-blind placebo-controlled food challenge of a cumulative dose of 1400 mg of peanut protein.⁶⁶

Alternative methods of immunotherapy, such as sublingual and epicutaneous immunotherapy have been trialled in a limited number of studies and have yet to be included as treatment options in clinical guidelines.⁶² Two trials by Kim et al. and Fleischer et al. studied sublingual immunotherapy in peanut allergy patients with 18 participants and 40 participants, respectively.^{67,68} Successful desensitisation was established in both studies compared to the placebo, with only mild occasional oropharyngeal symptoms reported in some patients.^{67,68} However, larger, more recent studies have focused primarily on (EPIT), with an international, multicentre, double-blind, randomised, placebo-controlled trial using a peanut patch applied daily for 12 months, with a total of 362 participants taking part in the study.⁶⁹ The primary efficacy end point was observed in 67% of children in the intervention group as compared with 33.5% of those in the placebo group ($p < 0.001$), while anaphylaxis occurred in 7.8% and 3.4%, respectively.⁶⁹ This large trial demonstrates the effectiveness and safety of EPIT in a population of toddlers 1-3 years of age, younger than the EAACI recommended age for immunotherapy of 4-5 years.⁶²

Egg oral immunotherapy

Fewer trials have been conducted on the effectiveness and safety of egg oral immunotherapy. A Cochrane review of 10 studies with differing OIT protocols found that most children (82%) in the oral immunotherapy group could ingest a partial serving of egg (1 g to 7.5 g) compared to 10% of control group children (RR 7.48, 95% CI 4.91 to 11.38; RD 0.73, 95% CI 0.67 to 0.80).⁷⁰ However, only 45% of children receiving oral immunotherapy were able to tolerate a full serving of egg compared to 10% of the control group (RR 4.25, 95% CI 2.77 to 6.53; RD 0.35, 95% CI 0.28 to 0.43). In addition, adverse events in the OIT group were common and occurred in all 10 studies. This included 21/249 (8.4%) of children in the OIT group requiring adrenaline compared to none in the control group as well as 75% of children

presenting with mild-to-severe adverse events during OIT treatment versus 6.8% of the control group (RR 8.35, 95% CI 5.31 to 13.12). While EAACI recommends egg OIT as a treatment option from 4 to 5 years of age, larger studies are required to establish a standardised protocol for egg OIT that is adequately safe and effective.

Milk oral immunotherapy

According to EAACI, OIT is recommended as a treatment option to increase the threshold of reaction while on treatment in children with persistent cow milk allergy, from around 4-5 years of age,⁶² based on evidence from its systematic review and meta-analysis.⁶³ Cow's milk OIT has been extensively trialled in several studies,⁶¹ including Keet et al. in 2012, who conducted a randomised trial to compare the safety and efficacy of oral immunotherapy and sublingual immunotherapy in the treatment of cow's milk allergy.⁷¹ All 28 participants were initially treated with sublingual immunotherapy for 6 weeks and were randomly divided into two groups for 60 weeks on maintenance dose.⁷¹ Half of them continued to receive sublingual immunotherapy while the other half continued oral immunotherapy. Those who received oral immunotherapy continued either 1 g or 2 g of cow's milk protein.⁷¹ Upon completion of the trial, those on sublingual therapy increased their tolerance to cow's milk protein by approximately 40-fold. Those who consumed 1 g in the oral immunotherapy group increased their tolerance by 54-fold and those who consumed 2 g of cow's milk protein, increased their tolerance by 159-fold.⁷¹ The results of this study demonstrated that although sublingual immunotherapy is successful at desensitising people who have a history of cow's milk allergy, oral immunotherapy is superior.⁷¹

Other foods and nuts

Oral immunotherapy in other allergenic foods such as walnuts, hazelnuts, sesame and wheat has also been investigated, albeit to a lesser extent.

Walnut allergy

In 2019, Elizur et al. recruited 73 participants between the ages of 4-17 years old with walnut allergy and introduced a graduated dose of walnut protein until a maintenance dose of 1200 mg daily was achieved.⁷² Of those in the oral immunotherapy group, 89% ($n = 55$, odds ratio 9.2, 95% CI 4.3-19.5; $p < 0.0001$) achieved desensitisation while none of the participants in the control group achieved desensitisation.⁷² All children co-allergic to pecan were also desensitised to pecan ($n = 46$). Furthermore, 60% (18/30) of participants who were co-allergic to cashews or hazelnuts and 93% (14/15) of participants who were co-allergic to hazelnuts alone, were shown to be partially or completely desensitised.⁷²

Hazelnut allergy

In 2020, Moraly et al. conducted a retrospective analysis of 100 patients aged 3-9 years with known hazelnut allergy in

a single-centre study who were introduced to 1635 mg of hazelnut protein (approximately 8 hazelnuts) as oral immunotherapy.⁷³ Of these 100 patients, 34% of the participants achieved desensitisation after 6 months (95%CI: 25–44).⁷³ Hazelnut SLIT has also been explored, where it was trialled among 23 patients who underwent an oral food challenge after 8 and 12 weeks of treatment.⁷⁴ Almost 50% of patients who underwent active treatment reached the highest dose (20 g), compared to 9% in the placebo, with only 0.2% of the total cohort experiencing systemic reactions.⁷⁴

Sesame allergy

Nachshon et al. in 2019 identified 60 patients, aged between 4 and 17 years, and introduced a starting dose of 1200 mg of sesame protein (equivalent to 5 g of tahini) to 60 participants in the exposure group.⁷⁵ It was reported that 88.4% (n = 53) of the participants were fully desensitised to sesame at 4000 mg and four participants were desensitised to more than 1000 mg of sesame protein.

Wheat allergy

In 2018, Nowak-Wegrzyn et al. carried out the first multicentre, double-blinded, placebo-controlled food challenge.⁷⁶ They recruited 46 participants with wheat allergy and were randomized into either a low-dose wheat exposure group or a placebo group.⁷⁶ After 1 year, 52.2% (n = 12) of participants achieved desensitisation to 4443 mg of wheat protein. At year 2, 20.4% (n = 7) achieved desensitisation to 7443 mg of wheat protein. None of the placebo participants achieved desensitisation.⁷⁶

These studies suggest oral immunotherapy is potentially a safe and effective option for desensitisation in egg, milk and peanut allergies.⁶² However, EAACI does not provide the same recommendation for other foods, including other tree nuts, wheat and fish due to the insufficient evidence to date.⁶²

New directions: Dietary advancement therapy for all stages of prevention

Dietary advancement therapies (DAT) include the ingestion of extensively heated allergens (including through progressive ladders) and are a distinguished new progression into the more active intervention of caregivers and physicians to support and hypothetically decrease possible food allergy in patients. It uses the early introduction of food in early life as a way of preventing the progression of desensitisation to allergy as well as promoting tolerance in IgE-mediated allergic patients. They therefore have the potential to be employed across the spectrum of primary, secondary and tertiary prevention of allergies.

The 'Egg and Milk Ladders' are widely used tools designed to induce tolerance in children with or at risk of egg or milk allergy.⁷⁹ They are home-based dietary advancements that gradually increase exposure to the allergenic food either in increasing quantities or allergenicity.⁶¹ It starts from extensively heated forms, such as

baked goods to the least processed product, such as milk or cracked eggshells.

The baking process alters the structure of allergens, changing their stability and subsequently creating decreased allergenicity (through decreased IgE binding). This is likely due to the destruction of conformational epitopes (antigenic determinants that bind with the IgE receptor) of milk and egg proteins.⁶¹ Several studies have reported a good tolerance response to baked milk (BM) introduction in children, even reporting accelerated tolerance to fresh milk.⁶¹ The three most recent studies of the milk ladder have demonstrated the effectiveness of the milk ladder in infants and children with IgE-mediated cow's milk protein allergy, with the success rate of participants ranging 86%,⁷⁸ 90%,⁷⁹ and 85%,⁸⁰ respectively. No incidences of serious adverse events of anaphylaxis were reported in these studies, demonstrating that the introduction of milk using the milk ladder can be safely used to promote tolerance in diagnosed IgE-mediated CMPA.^{78–80} In addition, an Irish study assessing the egg ladder, found it to be a safe and effective method of introducing eggs to children with both diagnosed IgE-mediated egg allergy as well as those with sensitisation to eggs, with only two of 29 children making no progress through the egg ladder over 1 year.⁸¹

The prevention of sensitisation and allergy was also demonstrated in the CORAL birth cohort, a cohort of babies born in Ireland during the first COVID-19 lockdown.⁸² Egg sensitisation at 12 months of age was greater in the pandemic cohort compared to a pre-pandemic cohort (5.8% vs. 3.7%, $p = 0.02$), while egg allergy at 12 months was greater in the pandemic cohort, but not statistically so (3.2% vs. 2.7%, $p = 0.6$).⁸³ However, this statistically significant difference was not present and in fact, egg sensitisation was slightly reduced at the 2-year follow-up (3.1% vs. 3.8% $p = 0.4$).⁸⁶ This reduction in egg sensitisation is likely due to the encouragement of parents of sensitised and allergic children to introduce eggs using the egg ladder.⁸⁴

Dietary advancement therapy in the form of milk and egg ladders has been employed as a method of both primary, secondary and tertiary prevention of allergies, particularly in Ireland, the UK and Canada.^{78,80,81,85,86} (Figure 3). Indeed, it supports the recommendations of current guidelines for the early introduction of foods to prevent food sensitisation and allergy.⁴² Further research among the paediatric population is recommended to establish the effectiveness, safety and compliance of these ladders, and indeed the adaptation of current ladders is encouraged to promote the introduction of these foods that are adapted to a wide range of diets, countries and cultures.

Conclusions

In the past, primary prevention of food allergies traditionally focussed on allergen avoidance. This led to abnormal and incomplete diets fuelled by fear of inducing food allergies. Several ground-breaking studies pioneered the introduction of food allergens early to prevent allergic sensitisation.

The challenge in conducting research on secondary allergy prevention lies with recruiting individuals after they have been allergen sensitised, but before developing a

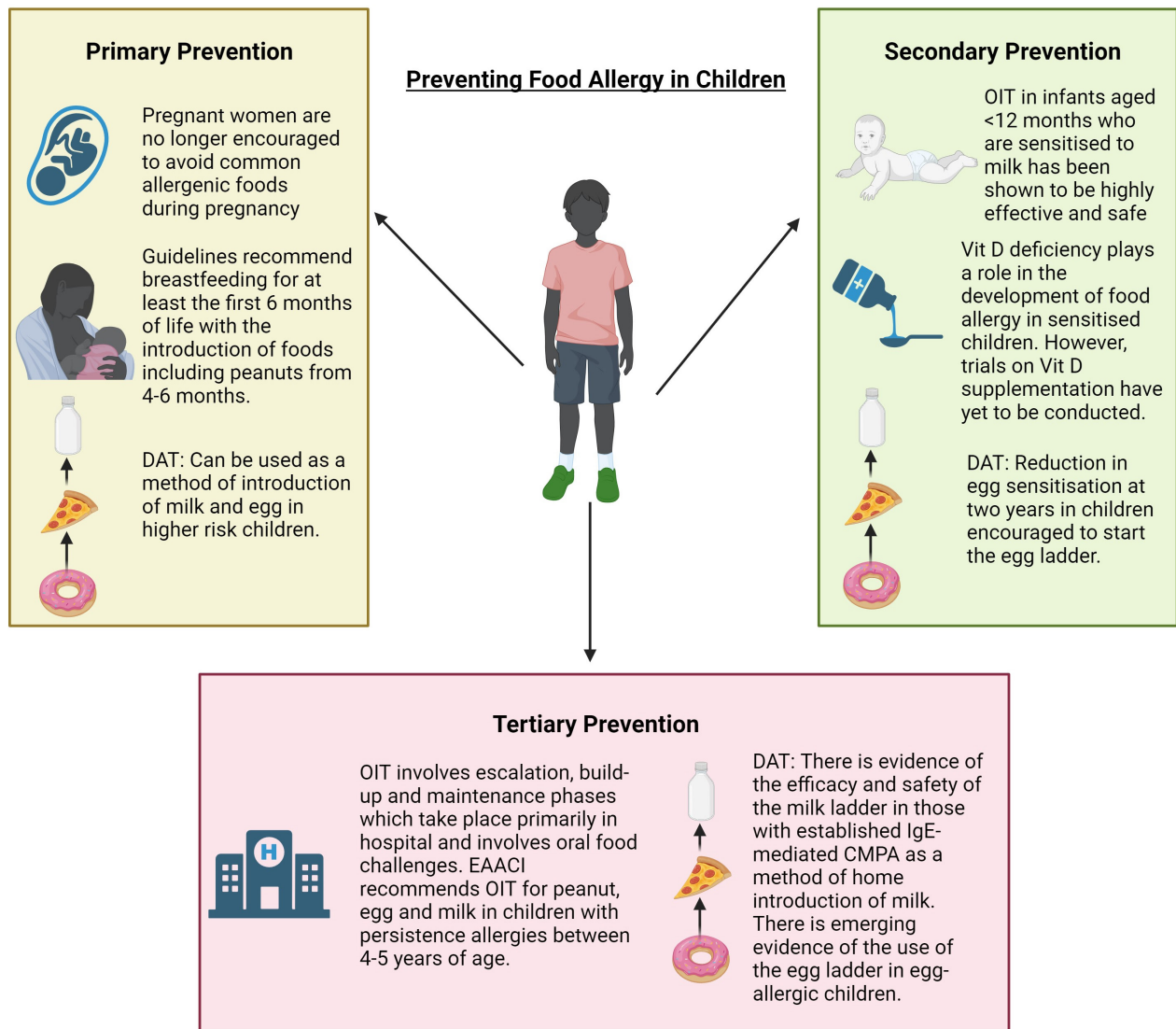


Figure 3. Summary of the methods of primary, secondary and tertiary prevention of food allergies, including the emerging evidence for dietary advancement therapy. DAT: dietary advancement therapy; OIT: oral immunotherapy; Vit D: vitamin D; EAACI: European Academy of Allergy and Clinical Immunology; CMPA: cow's milk protein allergy.

complete food allergy if they are not being tested regularly, it is incredibly challenging to establish. Therefore, instead of developing further secondary prevention practices, it might be more feasible in the future to combine these individuals with those undergoing tertiary prevention.

There is convincing evidence in support of tertiary prevention by means of oral immunotherapy. The research done till date indicates that this will be the main route of tertiary prevention moving forward. The primary limitation is the small sample size of participants in the randomised control trials. Although the protocols of these trials have so far proven to be safe, by participating in them, participants run the risk of undergoing an anaphylactic allergic reaction. Therefore, it is understandable that recruiting participants for oral immunotherapy trials will remain a challenge in the future.

Finally, dietary advancement therapy in the form of ladders has promising evidence for effective primary, secondary and tertiary milk and egg allergy prevention. Further studies are encouraged to adapt ladders for other food allergens as well as varied diets across the globe.

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Conflicts of interest

The authors do not have any conflicts of interest to report.

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