Review Article

ALLERGY PREVENTION – REALITY OR NOT?

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ABSTRACT

While the epidemic of respiratory allergy (asthma and rhinitis) which began 50–60 years ago has begun to taper off in some parts of the world, most notably in affluent countries, a second wave involving food allergy and atopic dermatitis is in full swing. Once established allergic diseases, while episodic with changing manifestations over time, last for decades and are often lifelong. The number of lives affected and the quality of life implications mandates investigation of interventions to mitigate these conditions which together constitute the commonest long-term disorders to affect young people. The health economic burden of allergic diseases is considerable and as new biological therapies are approved this will only increase. The search for a cure has hitherto been fruitless but there is the hope that by understanding basic mechanisms it will eventually be possible to design targeted biological therapies to switch off the allergic process. However, this is an expensive enterprise and the costs of curative treatment may well be prohibitive. Prevention has become a focus for many long-term conditions and allergic disease must be included given the potential that strategies will confer considerable health/economic benefits. Health promotion which emphasises avoidance of environmental tobacco smoke, alcohol, pollution and obesity with promotion of exercise, and a nutritious diet has implications for allergic disease as well as the usual focus on cardio-vascular disease, cancer and metabolic syndrome.

There are four potential 'windows of opportunity' in early life which impact on the genetic potential to develop allergy in young children. They are in line with the developmental origins of health and disease hypothesis often now known as the first 1 000 days from conception to the second birthday.

Published studies of factors influencing the ontogeny and prevention of allergy have shown very different outcomes which makes careful attention to design and methodology critical. Most publications conflate diverse phenotypes each of which are associated with different gene/environment interactions. Allergic sensitisation must be considered separately from allergic disease. Atopic dermatitis/eczema, asthma, rhinitis, food, drug and insect venom allergy all have separate genetic and environmental influences. Many studies are underpowered to account for all the likely confounding factors. Some focus only on so-called 'high-risk families' with parental allergic disease, whereas others study whole populations.

Notwithstanding these concerns, it is our firm belief that by combining interventions we should be able to offer a basket of 'allergy-prevention' strategies both for high-risk families and whole populations. The interventions will confer benefits for many long-term conditions.

Keywords: allergy, eczema, asthma, rhinitis, food allergy, prevention, cure, high and low risk families

INTRODUCTION

Allergic diseases affect more people than any other group of chronic conditions. In addition, for most allergic conditions the prevalence in many countries of the world is still increasing though asthma and allergic rhinitis (AR) changing prevalence has reached a plateau and may even be decreasing in a few countries. In a CDC/NHLS survey reported in 2013, both food allergy and atopic dermatitis/eczema (AD) are still rising in prevalence dramatically.[1] This suggests that the allergy epidemic has occurred in two phases. The respiratory epidemic has generally plateaued in developed nations or even declined in places, however, food allergies as the second wave of the epidemic, are generally still rising. In most developing nations all the allergic diseases are still increasing in prevalence. The disconnect in timing of prevalence changes for inhalant and ingestant allergies suggest that different gene/environment interactions are involved. It is reasonable to suggest that in the face of this mounting threat to health, with its attendant morbidity, impaired quality of life (QoL), cost and even mortality, we should urgently explore potential cures for these conditions, but, based on current evidence, a strategy for prevention may be more attainable.

The quote 'prevention is better than cure' is often attributed to the Dutch philosopher Desiderius Erasmus from around 1500. Health promotion and disease prevention are a focus for policy worldwide, but are underused, partly because evidence is difficult to generate. There are, however, strong arguments for very simple strategies to improve health and well-being, which are cost-effective by comparison with established healthcare.[2] These have been focused on the early years of life which have become known as 'the first 1 000 days, from conception to 2 years of age'.

WINDOWS OF OPPORTUNITY FOR PREVENTION

In relation to allergy there are four likely windows of opportunity for intervention which overlap with one another. Primary prevention or prophylaxis is instituted before allergic sensitisation has occurred and focuses on pregnancy and the neonatal period. Secondary prophylaxis commences after sensitisation but before disease onset or when the first manifestations of AD have occurred and commences around 2–4 months of age. Tertiary prophylaxis is used to prevent the evolution of food allergy and AD into AR and asthma, to inhibit the so-called 'Allergic March'. Quaternary prophylaxis is conventionally viewed as the use of disease-controlling therapies such as inhaled steroids, but other than allergen immunotherapy, none impact on the natural history of allergic diseases. In this article we will discuss only those specifics related to allergy rather than conventional disease-controlling pharmacotherapy.

There is evidence that interventions may be possible in each of the four windows in order to reduce the risk of allergy induction and disease development. Some interventions have been tested in randomised trials, but many have hitherto been suggested based only on observational studies showing associations between various factors and disease occurrence. These association studies cannot necessarily be translated into causation or in proving no effect, as they are often subject to confounding. An example is that studies of breastfeeding have not provided convincing evidence of allergy prevention but are confounded by breastfeeding being more likely to be employed by those with a strong family history of allergic disease.[3]

Several mechanisms explain gene–environment interactions. Asthma has provided many examples of polymorphisms for instance in antioxidant genes which are expressed as airway disease only if there has also been environmental tobacco smoke (ETS), pollutant or paracetamol exposure.[4,5,6] The environmental factors increase oxidative stress and if regulatory mechanisms are defective due to gene polymorphisms, airway inflammation will evolve. Likewise, polymorphisms in allergy-promoting genes (cytokine gene cluster, MHC, variable regions of T-cell receptor, IgE receptor) are only expressed when allergen exposure occurs at critical time periods in early life.[7]

Epigenetics has more recently provided an explanation for mechanisms by which very subtle changes in environment affect gene expression without modifying DNA sequences. Many environmental factors have been shown to increase methylation of CpG DNA sequences which silences gene expression, or a range of chemical moieties which attach to histones around which DNA winds. The latter tends to unwind DNA and increase expression. These changes to gene expression are transmissible across generations.[8] One of the best examples of an epigenetic transgenerational effect is of the demonstration that grand-maternal smoking increases asthma in grandchildren irrespective of maternal smoking.[9] This extends allergy prevention strategies to at least a generation before conception. The single largest avoidable health hazard for the world's population is environmental tobacco smoke, which, if avoided, would reduce a huge number of serious health and life-threatening problems including asthma.

This article addresses some of the studies where allergy prevention has been attempted and will try to balance the many conflicting outcomes in the literature.

THE BASIC PROBLEM WITH ALLERGY-PREVENTION STUDIES

There are longitudinal cohort observational studies that report both positive and negative associations with specific environmental exposures. In addition, intervention studies have found either positive or negative outcomes. Often the observational studies show large effects while intervention trials have very much less or no impact on allergic outcomes. How can we explain these differences?

The outcomes reported in studies variously include positive allergy tests, and/or AD, and/or asthma, and/or rhinitis, and/or food allergy. Allergic sensitisation is not synonymous with allergic disease and each disease has different gene/environment influences. Different endpoints will therefore be likely to generate different association results. Observation studies often rely on a history of symptoms suggestive of AD, asthma, rhinitis and food allergy or prior doctor-diagnosed conditions. Wheeze is caused by many conditions other than asthma, an itchy rash is not necessarily AD and families often misinterpret reactions to food as having an allergic cause. Clinical histories require greater precision preferably combined with appropriate allergy tests, but few studies have achieved this.

Studies have sometimes focused on high-risk families imprecisely defined as either 1 or 2 parents and/or siblings with allergic diseases often based on history only. Attempts to find a biomarker of risk have been disappointing. Raised cord-blood IgE levels are reasonably predictive of later allergy but most future-allergic children have undetectable IgE at birth.[10] Monitoring the changing balance of T-lymphocyte helper 1 and 2 (Th1Th2) cell responses may be more specific and sensitive but are costly, labour-intensive and not used in large studies. Other publications have recruited whole population cohorts sometimes reinforced with high-risk families. The age of recruitment has varied, the timing of the final endpoint and frequency of observation is inconsistent. Understanding of the natural history of allergic diseases makes it clear that studies should commence in pregnancy and continue ideally to well beyond five years when most allergic conditions will have manifested.

Observational studies must be sufficiently large to facilitate statistical analysis which account for the many confounding factors. Intervention studies must be sufficiently powered to avoid type 1 and 2 errors. Selection must be precise as

outcomes could be very different dependent on the degree of risk of the population included.[11]

ALLERGY-PREVENTION WINDOWS DEFINED

Allergy prevention strategies operate in many different time frames. There are certain clearly defined periods in which factors impact on the allergic march and could be viewed as ‘‘windows of opportunity” during which strategies could prevent allergy or inhibit its progress.

These windows are not the only place where intervention works, there is overlap in timing between each window which may extend beyond 1 000 days and it is not implied that if a window is missed, nothing more can be done to prevent a child from becoming allergic. However, for reasons of simplicity, we have gathered the evidence for what may work in these four windows which can be described as primary, secondary, tertiary and quaternary prophylaxis.

While some of the interventions have been tested in randomised trials, others are suggested based only on evidence demonstrating association between factors and disease occurrence. For some interventions which might have preventive properties it is next to impossible to conduct controlled clinical trials – such as is the case with breastfeeding. Relying on outcomes based on parental choice of mode of feeding has many potential confounders. We present the evidence in each of these windows and try to balance interventions that reduce allergy with those that show no or little effect.

WINDOW 1 – PRIMARY PROPHYLAXIS

Pregnancy is from an immunological perspective akin to a transplant because the fetus expresses both paternal and maternal antigens to which maternal Th1 responses should induce fetal rejection. That this does not occur is in part due to a Th2 cytokine profile generated by decidual tissues which downregulates maternal Th1 responses. Additional modulation of the maternal Th1 response is affected by T-regulatory cytokines and the expression of a monomorphic tissue type (HLA-G) at the feto–maternal interface. Amniotic fluid also contains antigens/allergens to which the mother has been exposed and combined with Th2 cytokines induces sensitisation through fetal swallowing in the small intestine.[12] All newborns have a Th2-biased immune response though some balancing occurs in the third trimester when IgG antibodies actively transported from mother to fetus, which if specific for allergens will downregulate immune responses. High levels of IgG antibody in cord blood to egg, cat and dog, due to high maternal exposure, have been shown to be associated with less subsequent allergy to those allergens.[13,14] Allergen immunotherapy continued during pregnancy which increases IgG antibodies is also associated with less subsequent allergy in the offspring.[15] There is a bell-shaped curve of risk of sensitisation in relation to levels of allergen exposure in pregnancy. Very low levels are insufficient to induce sensitisation while very high levels induce tolerance through a range of mechanisms. As complete avoidance is rarely achievable high exposure may be a more practical strategy. However, controlled trials are required and for the present the advice must be to continue as normal rather than to avoid any potential allergen for primary prevention.

Diet during pregnancy also has effects on outcomes. Several cohort studies have suggested that high fish, fresh fruit and vegetable intake is associated with less asthma in offspring. However, intervention trials using n-3 PUFA supplementation have had disappointing little effect on allergic outcomes.[16] Similar results are apparent from studies of vitamin D intake in pregnancy. Observational cohorts suggest an association between insufficiency and more asthma while intervention trials of supplementation have shown no effect.[17,18] The greatest beneficial effect is seen with the so-called ‘Mediterranean diet’.[19] This suggests that it is not individual constituents of the diet but the panoply of ingredients which have impact. Therefore, a healthy balanced diet is the most appropriate recommendation. Obesity in the mother increases the risk of a caesarean section delivery and with offspring obesity. These factors in turn increase the risk of food allergy and asthma.[20,21] Overweight future mothers should enter weight-reduction programmes preferably preconception with increased exercise and calorie control.

Avoidance of pregnancy smoking is important for many compelling reasons and may also reduce the risk of asthma in offspring. Based on the epigenetic effect it may take two generations for an impact of avoidance to be detected.[9] Avoidance of frequent paracetamol use in pregnancy would also be sensible, however, an adverse effect may manifest only in association with maternal genetic polymorphisms in anti-oxidant genes.[5] To what extent other inhalant pollutants have an impact during pregnancy remains to be established but there are many health-protection reasons for promoting clean-air legislation including direct adverse effects on those with asthma.

The other strategies during pregnancy are preparation for delivery and the neonatal period. This includes avoidance

TABLE I: FACTORS THAT MAY BE INTRODUCED IN PREGNANCY TO MITIGATE ALLERGY RISK

- Polyunsaturated fatty acid supplementation (fish oil supplementation) – reduction in AD and wheeze in children in at least one study.
- Probiotic use demonstrates conflicting evidence but may reduce AD in offspring.
- Vitamin D supplementation. No evidence demonstrated, but theoretical benefit from regular sunlight exposure.
- Regular exercise and healthy diet.
- **Avoid smoking (smoking associated with allergy, wheeze, asthma and infection risk).**
- Plan for vaginal birth and breastfeeding.
- Start thinking of strategies for postnatal allergy prevention.
- Keep maternal allergic conditions well controlled to avoid pregnancy complications.
- Reduce maternal stress which otherwise increases neonatal allergic disease in animal studies and asthma in human beings.
- Avoid prenatal antibiotic and paracetamol exposure which are associated with an increased risk of asthma.

of antibiotics – if possible – as they will alter the maternal microbiome and therefore impact on seeding of the neonate's microbiome during a normal delivery.[22] Trials of pre- and pro-biotics administered during pregnancy have been combined with continuation in the postnatal period.[23] The effects of prenatal manipulation of maternal microbiome alone has not been submitted to a separate study.

The birthing process is probably a significant factor in primary allergy prevention. Large epidemiological association studies have shown benefits associated with normal vaginal delivery and risk of allergic (and multiple other chronic inflammatory) diseases associated with elective caesarean section which was associated with increased risk for a number of long-term conditions[24] (see Table II).

TABLE II: RISK OF CHRONIC CONDITIONS IN CHILDREN BORN BY CAESAREAN SECTION[24]

DISEASE OUTCOME	CASES	aHR	p-VALUE
Asthma	103 822	1.23	<0.0001
Systemic connective tissue disorder	7 498	1.11	0.0021
Juvenile arthritis	6 946	1.10	0.0021
Inflammatory bowel disease (IBD)	2 697	1.20	0.004
Immune deficiencies	2 589	1.46	0.0001
Arm fracture*	77 490	0.99	0.19

*Arm fracture included as a control group.

In the Swedish Birth Cohort Study of more than a million children, during the 13-year follow-up, 26 732 (25%) children had a diagnosis of food allergy which was positively associated with caesarean delivery (HR, 1.21; 95%CI, 1.18–1.25).[20] A meta-analysis of caesarean section studies has shown some consistency of adverse allergic outcomes[25] but not all have shown an effect.[26]

The hypothesis underlying the effect of delivery is related to the establishment of a normal infant microbiome. This is achieved through seeding of maternal bacterial flora during a normal vaginal delivery. Provided the mother has a healthy microbiome, the neonate should also achieve what is known as 'eubiosis'.[27] As all neonates have a Th2-biased cellular response balance is achieved through the impact of particularly the gut microbiome in inducing both Th1 and T-cell regulatory activity. This is achieved through a rapid diversification of microbial species in the infant gut. Reduced diversification is associated with a higher risk of eczema.[28] The third highest group of constituents in human breast milk are prebiotic oligosaccharides which have immune modulatory properties and promote eubiosis.[29] Attempts to promote a normal microbiome particularly in bottle-fed infants have involved the use of pro- and pre-biotics. Intervention trials have produced conflicting results probably because we still do not understand enough about what constitutes a healthy microbiome. Nevertheless, one of the largest trials of pre-biotics given to milk-formula-fed infants showed reduced AD over the first year of life.[30]

The role of exclusive breastfeeding remains uncertain in allergy prevention. Based exclusively on observational studies the association between breastfeeding and AD have suggested a protective effect, with weak effect on AD and a stronger effect on asthma from a systematic review and meta-analysis.[31]

The main problem is that breast milk is not a uniform substance. There are many constituents which vary over time and between mothers dependent on their health and environment. In particular there are differences in levels of pre-biotic oligosaccharides which affect the gut microbiome and of immune modulatory cytokines.[3] The most recent study showed lower levels of short-chain fatty acids (SCFAs) in the milk of atopic compared with non-atopic mothers.[32] SCFAs are a product of bacterial digestion of dietary fibre and have immune modulatory properties including stimulation of regulatory T-cell activity. Future studies will need to account for these variations with the potential to identify interventions which will fortify the allergy preventive effects of breastfeeding. In the meantime breastfeeding has so many benefits that it must always be part of a health-promotion strategy.[33,34]

A more controversial allergy-prevention strategy is the use of hydrolysed milk formulae. The excellent GINI study demonstrated a reduction in AD using both partially hydrolysed whey and extensively hydrolysed casein formulae, even up to 15 years of age but it had no effect on allergy.[35] Three recent meta-analyses have been predominantly negative[36-38] (see Table III).

TABLE III: META-ANALYSES OF INTERVENTIONS WITH HYDROLYSED FORMULAE TO PREVENT ATOPIC DERMATITIS

	Boyle BMJ 2016[36]	Szajewska WAO Journal 2017[37]	Cochrane Review 2018[38]
Published	2015	2016	2017
Included studies	RCT/CT	RCT	RCT & quasi RCT
Material studied	All hydrolysed formula	Only 100% pH whey	HF vs CMF or HM-
Conclusion	No consistent evidence to support the use of hydrolysed formula for the prevention of allergic disease.	Both ITT and PP analyses showed that the reduction was statistically significant at some, albeit not all, time points.	No evidence to support short-term or prolonged feeding with a HF compared with a cow's milk formula for prevention of allergic disease.

Abbreviations: RCT – randomised controlled trial; CT – controlled trial; pH – partially hydrolysed, ITT – intention to treat; PP – per protocol.

The conclusion at present is that hydrolysed milk formulae should not be included in an allergy-prevention programme but maybe in those unable to breastfeed prebiotic supplementation of formulae might have value.[30] It remains to be seen whether SCFA supplements will add benefit.

WINDOW 2 – SECONDARY PROPHYLAXISs

Few studies have investigated strategies to prevent the evolution of allergic sensitisation into allergic disease. This is established in the evolution of occupational allergic-airway

disease. Sensitisation to the occupational allergen after a period of exposure is followed first by rhinitis and skin manifestations. If detected and avoidance is instituted at this stage disease is avoided. This approach merges into tertiary prophylaxis because asthma develops after more sustained exposures. Provided avoidance is instituted early, asthma can be prevented or completely resolved despite allergic sensitisation. However, if exposure continues asthma eventually becomes entrenched and will continue even if the occupational allergen is avoided.[39] If this sequence occurs in allergic asthma, as is very likely, then early avoidance of the primary allergic trigger could have much greater benefit than has been achieved once asthma is established and particularly if it has reached a chronic stage with structural (remodelling) changes to the airway wall. This approach requires further research trials.

The underlying genetic associations with AD are those effecting epidermal barrier function. The most widely studied are polymorphisms in the Filaggrin gene[40] and there is strong evidence that they facilitate allergic sensitisation to foods and inhalants through the skin.[41,42] This has led to studies of prophylactic emollients to reinforce the skin barrier with equivocal results.[43–45] However, the main association between skin-barrier defects and sensitisation to allergens is apparent only in those who have already developed AD. The inflammation in association with the epidermal barrier defect increases the likelihood of sensitisation to any allergens coming into skin contact. Food allergy is more likely to be caused by AD rather than the previous conventional view of the allergic march.[46] This has led to the concept of inducing tolerance to foods before skin contact results in sensitisation.

For foods early exposure from four months of age in the gut – preferably in association with ongoing breastfeeding and an appropriate microbiome – provides the best opportunity to achieve tolerance. This is the basis for what is known as the LEAP study (Learning Early About Peanut). Peanut exposure demonstrated both a primary and secondary prevention benefit for peanut allergy. It reduced subsequent acute peanut allergy in infants with eczema and/or egg allergy in those without evidence of peanut allergy but also in those with weakly positive allergy skin tests to peanut at recruitment[47] (see Figure 1). The implication is that early peanut ingestion induced tolerance in those not yet sensitised and sensitised T-cell deletion in those already sensitised.

The following year the EAT study revealed no protection from a combination of early exposures to six common allergenic food in the intention to treat population (see Figure 2).[48] However, adherence to early feeding was 42.8%, whereas for standard feeding it was 92.9%, suggested that, at least in part, one of the problems of early weaning studies is that the early introduction of diverse foods is difficult to achieve, and maybe parental concern also impacted on weaning practice. The per protocol analysis showed benefits for early peanut and egg but notably not milk. A review of published evidence provides strong support for early (4–6 months) egg introduction, limited support for peanut because this is based on two exclusive studies in the United Kingdom. For all other common allergens there has been insufficient evidence hitherto and the meta-analysis for milk has showed no effect.[49]

Much has been made of the potential role for pro- and pre-biotic supplementation in preventing allergy. Conflicting literature has shown some studies supporting the benefit of pro- and pre-biotics in prevention, whereas other studies show no effect. Heterogeneity of study design mitigates against forming an evidence-based opinion.[50] The ultimate answer to the strategy may well depend on the bacterial strains employed, dose and timing of intervention. At least for the prevention of necrotising enterocolitis (NEC) in pre-term infants multiple-strain probiotics are most effective.[51]

WINDOW 3 – TERTIARY PROPHYLAXIS

Allergen immunotherapy is a specific approach to tertiary prophylaxis. It has been shown interrupt the allergic march from seasonal AR to asthma and has a sustained effect for some years following cessation of treatment after three years.[52,53]

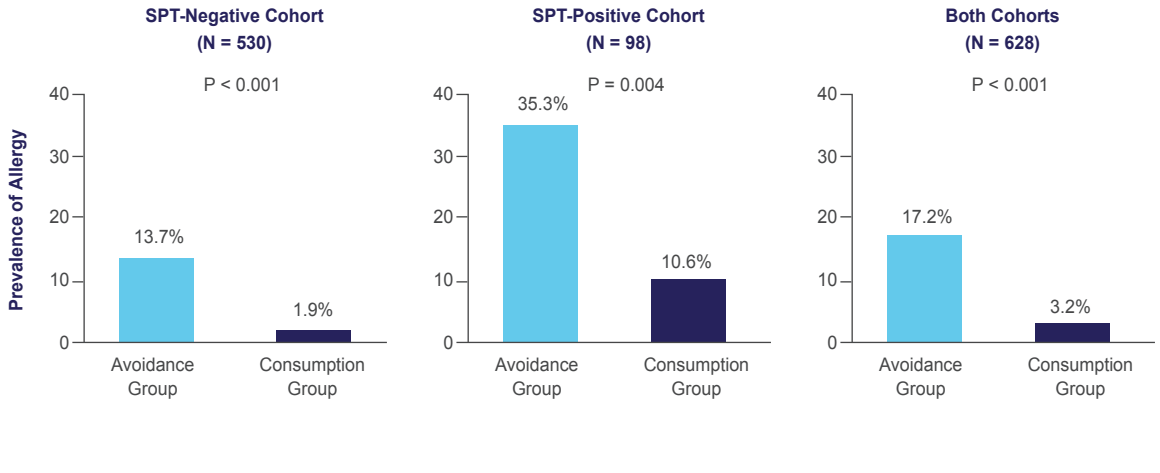

Figure 1: Results of the LEAP study

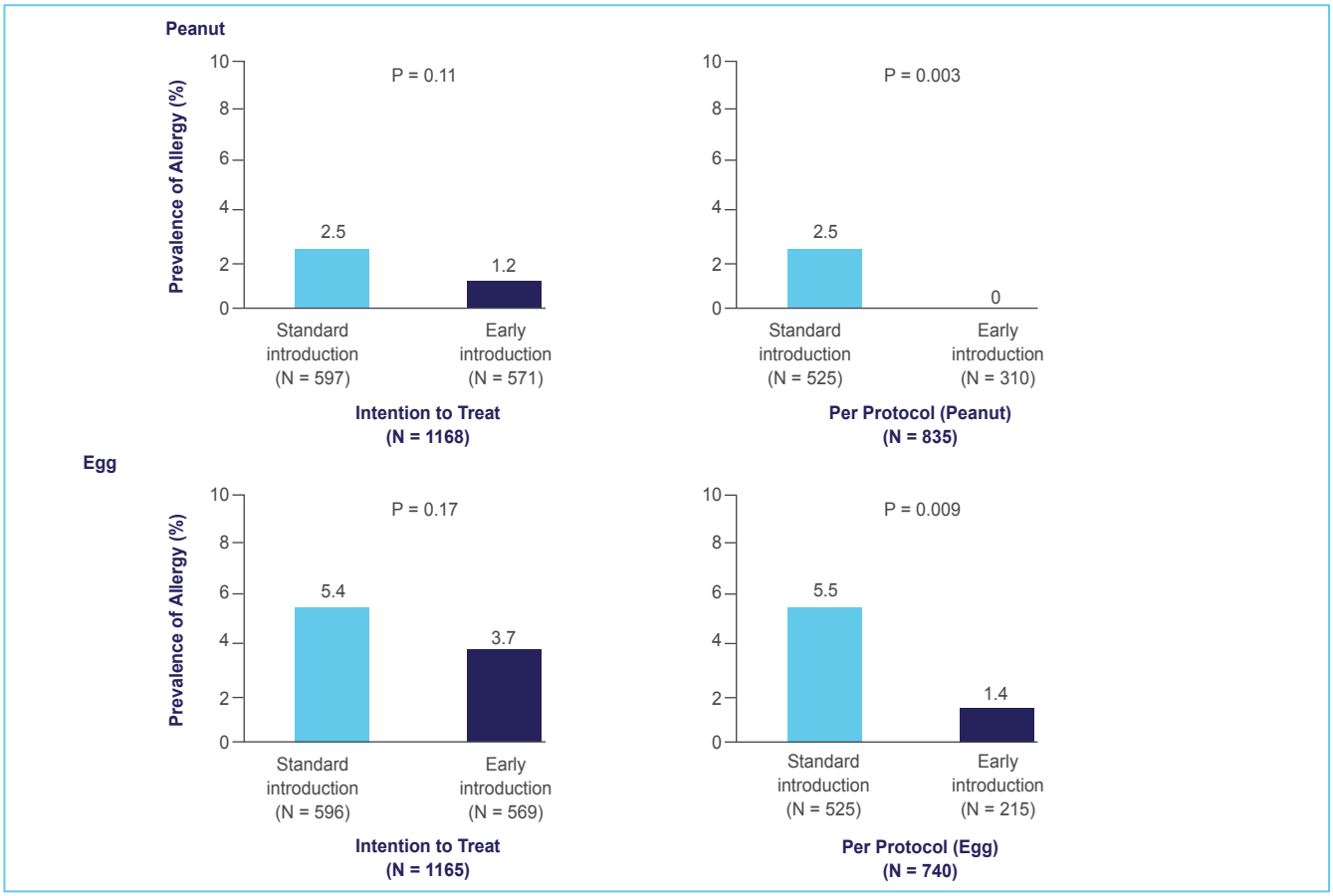

Figure 2: Results of the EAT study

Commencing allergen immunotherapy in those with a single-inhalant allergy reduces the probability of developing new allergen sensitisations.[54]

There have also been attempts at pharmaco-therapeutic approaches to inhibiting the allergic march using second-generation antihistamines which impair allergen-induced eosinophil migration. The results have been at best equivocal but at least are a safe approach with direct benefits from their use in infants with AD.[55] No other form of pharmaco-therapy has true prophylactic properties.

WINDOW 4 – QUATERNARY PROPHYLAXIS

As allergen exposure aggravates pre-existing allergic disease allergen avoidance should be of benefit. However, many trials have failed to demonstrate consistent efficacy, particularly in relation to house-dust mite (HDM) allergic asthma/rhinitis. This has led to Cochrane systematic reviews reaching the conclusion that allergen avoidance has no place in therapeutic algorithms.[56] The difficulty is that exposures occur in many places, and strategies to reduce aeroallergen levels, whether to HDM, animals, pollens or moulds, have been insufficient. Recent trials of an effective environmental control system, based on temperature-controlled laminar airflow, employed overnight, have shown significant improvements in QoL and eosinophilic airway inflammation (represented by raised exhaled nitric oxide levels) in severe asthma in children and adults.[57,58] While guidelines for asthma management have tended – mistakenly in our view – to consider allergen avoidance as secondary to pharmacotherapy, those for rhinitis have given this approach a higher priority.

In patients with food allergy, the standard practice is avoidance of the offending food(s) but as this is difficult to achieve treatment must be immediately available to deal with accidental exposures. Other than for occupational allergic disease there is no evidence that early allergen avoidance modifies long-term outcomes.

After allergen avoidance, allergen immunotherapy is the other specific approach to quaternary prophylaxis. However, severe and very occasional fatal allergic reactions to the therapy occurred in some patients, most notably in those with severe asthma. Unfavourable comparisons with relatively safe pharmacotherapy for asthma and rhinitis relegated its use to severe insect-venom allergy and AR alone. There is no doubting the efficacy of inhalant allergen immunotherapy in directly reducing allergic reactions and it is the only approach which modifies the natural history. Cochrane reviews have shown benefits in improving asthma symptoms, reducing treatment requirements and bronchial hyper-responsiveness.[59] Furthermore, treatment for three years is often followed by a sustained benefit for several years after cessation of treatment.[60] The immunotherapy approach has also been used in acute food allergy and has sometimes been labelled systemic oral tolerance induction (SOTI). The principle of administering progressively increasing

doses of the allergen is similar for all allergen immunotherapy but hitherto has involved relatively unmodified food proteins with inevitable acute allergic reactions during treatment.[61] The advent of allergen modification, co-administration of immune modulators and alternate routes of administration may make this approach more clinically acceptable.[62] While for inhalant allergy three years of immunotherapy is enough in the majority to produce long-term benefits, there is insufficient evidence to establish when true tolerance, with carry-over beyond the end of treatment, has been achieved for food allergy.

CONCLUSION

As we are in the midst of the allergy epidemic, we strongly support renewed efforts for consensus on allergy-prevention strategies within potential windows of opportunity. There is evolving evidence that health-promotion strategies are likely to impact on allergic disease prevalence as well as cardiovascular, metabolic and other common long-term conditions.

Primary prevention occurs through several time points. Pre-conception priorities are avoiding environmental tobacco smoke and other air pollutants with the latter being more in the remit of politicians. A diverse healthy diet and regular exercise is an imperative for all but particularly important to achieve weight reduction in those who are overweight. The healthy diet and exercise should be sustained throughout pregnancy including fish, fresh fruit and vegetables. There is no place for food or inhalant-allergen avoidance and, if anything, a normal to high intake is appropriate. Maintenance of a high normal vitamin D level is important, ideally through sunlight exposure but if not possible a dietary supplement. If possible, the use of antibiotics and paracetamol should be avoided. Caesarean section delivery should be minimised and is indicated only for good medical reasons. If truly needed the use of pro- and/or pre-biotics may mitigate some of the adverse effects. While the evidence that exclusive breastfeeding reduces allergy is equivocal, there are many reasons to include it as a key component of primary prevention. Optimising maternal health and environment to improve the protective properties of human milk should be a focus for research.

Secondary prophylaxis is currently focused on infants who have either developed AD or are sensitised but not yet allergic to peanut or egg. Early introduction of peanut and egg into the diet from 3–4 months of age reduces the subsequent prevalence of allergy to these foods, but care must be taken in those who already have signs of allergic disease, such as those infants with severe eczema, who need thorough assessment before advising allergen introduction. It is not yet known whether this can be extrapolated to other common allergenic foods. However, there is no reason to delay their introduction during normal weaning, preferably overlapping with continued breastfeeding.

Tertiary prophylaxis to inhibit the allergic march from AD/food allergy and/or rhinitis to asthma involves attempts at tolerance induction. This is achievable by pollen allergen immunotherapy in those with seasonal AR but no asthma. It remains to be seen whether early food allergen immunotherapy will achieve the same effect.

No pharmacotherapy has been shown to alter the natural history of allergic diseases Therefore, we believe that quaternary prophylaxis is either achieved through allergen avoidance which for occupationally induced disease is highly effective provided it is introduced early. There are effective devices to reduce aeroallergen exposure using temperature-controlled laminar airflow. Inhalant allergen immunotherapy has been shown to have a sustained effect for many years after cessation of therapy.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

This article has been peer reviewed.

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