Review Article

# ALLERGY PREVENTION: SOMETHING OLD, SOMETHING NEW, SOMETHING BORROWED, SOMETHING BLUE

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## ABSTRACT

The significant burden of allergic disease worldwide and lack of a cure for allergies make prevention an attractive strategy. With increased understanding of the nuances of allergic sensitisation, we are moving away from the concept of "strict allergen avoidance" towards the method of "tolerance induction."

Progress has been made in the past decade which can now promote maintenance of skin barrier integrity, enhancement of infant gut microbial health and promotion of oral tolerance by earlier oral introduction of allergenic solids as effective allergy prevention strategies.

## INTRODUCTION

The prevalence food allergy, eczema and respiratory allergies has increased substantially in the past 3-4 decades.[1-3] These conditions cause significant morbidity, and to a large degree have no "cure," hence a significant effort has been put into researching the primary prevention of allergies in the past few decades.

Pregnancy is essentially a T helper Type 2 (Th2) lymphocyte-dominant regulatory environment to counteract the potentially harmful maternal Th1 response against feto-paternal antigens.[4] The Th2 skewed response in the foetus needs to switch to a more balanced Th1/Th2 milieu post-partum to prevent immunological swaying towards allergies. Factors which are key to this switching process include parental allergy, timing and quantity of allergen exposure, antibiotic exposure, nutrition, maternal gut microbiome and microbial diversity in the infant. Changing patterns of exposure to antigens (including infectious agents, food allergens, and aeroallergens) as people adopt more modern living environments and lifestyles may well promote allergic phenotypes.[5]

Allergy prevention strategies can be targeted at the times of pregnancy, lactation, early infancy and complementary feed introduction. The window of opportunity for intervention seems to be largely completed by 6-7 months of age. We previously discussed allergy prevention strategies in this journal in 2012.[6] Although the general advice provided at that time still holds true, several new preventive strategies have been explored or published in the past 3 years. This article serves to reinforce the current preventive strategies which have enough of an evidence base to be recommended in daily practice; and also to discuss newer prevention studies from the past 3 years.

The old wedding adage encouraging a bride to wear "something old, something new, something borrowed and something blue" aptly describes the different facets of this review article. I shall start with "something blue"- which is the bad news; the current reality of high allergy prevalence. "Something old" will discuss the "old" strategies which are completely outdated, as well as the "older" strategies which still hold true. "Something new" will look into some of the latest research in the allergy prevention world, which has been based on several "borrowed" principles.

This article will focus on prevention of atopic dermatitis (often considered the "kindling wood" of the allergic march) as well as food allergy.

## "SOMETHING BLUE"

Food allergy and atopic dermatitis (AD) impose a significant reduction in quality of life and burden on the healthcare system.[7] Up to 20% of children in wealthy countries have AD, and up to 10% have at least one food allergy.[2,8]

The rapid increase in allergies in many parts of the world cannot be explained by genetic mutations alone, but represent a complex interaction between genetic and

environmental factors. The multitude of interacting events, acting prenatally and postnatally, make allergy prevention studies complex and often difficult to compare. Several studies, which initially provided exciting prospects, have been negated by subsequent similar studies with less promising results. The results of postnatal manipulation have thus far been disappointing, with even the protective effect of breastfeeding being more inconclusive in recent studies.[9]

In the past few years the concept of epigenetics has wormed its way into mainstream allergy prevalence literature.[10] Epigenetics elaborates on the way in which the environment, of which nutrition may be critical, changes the way genes are expressed, without directly changing the gene DNA sequence. Epigenetic changes are critical in early life to influence immune programming and effect the expression of disease. Our attempts to influence epigenetics have been largely unsuccessful in the past few decades.

The power of environmental influences acting on gene expression is demonstrated in studies of migrant populations. First generation adult immigrants from countries with low allergy prevalence to those with higher prevalence retain their low allergy rates, however, when children of these immigrants are born in a higher prevalence country, they have a higher allergy prevalence matching or even exceeding that of the local population.[11] This is also one of our concerns in the local South African context: we fear that an "allergy epidemic" will escalate as indigenous Black populations leave their traditional protective cultures to take on a more westernised lifestyle, making them susceptible to more "westernised" expression of disease such as allergies.[3,12] This may still spell a significant local public health crisis.

## "SOMETHING OLD AND OVER THE HILL"

Observational data has suggested that the general trend towards later introduction of solids in the past few decades has coincided with a 2-3 fold increase in childhood atopic dermatitis.[13,14] Food allergies are a rare phenomenon in societies in which allergenic foods such as peanut are introduced early.[15]

With increased understanding of the nuances of allergic sensitisation, we are moving away from "strict allergen avoidance" towards the method of "tolerance induction."

Gone are the days of advising maternal elimination of allergenic foods during pregnancy, lactation, and indeed also withholding allergenic foods during solids introduction to the infant. The old concepts of "no dairy for 1 year, no egg for 2 years and no nuts or fish for 3 years" are now in the archive room and should not be advised in any preventive capacity at all.

Prominent paediatric societies such as the American Academy of Paediatrics (AAP), as well as the European Academy of Allergy and Clinical Immunology (EAACI), have withdrawn all recommendations of allergen avoidance during pregnancy and lactation and indeed in the infant. This revision of these recommendations was already implemented in 2008. However, 7 years down the line, incorrect information is still being distributed at many levels of health care, probably to the detriment of our children.

We all have a responsibility to be on board with the newer advice on allergenic foods and allergy prevention, and disseminate it at all levels of health care.

## "SOMETHING OLD BUT STILL HOLDS"

The EAACI food allergy and anaphylaxis guidelines for primary prevention of food allergy in children and adults were published in 2014 based on an extensive systematic review.[16] With a more American readership, the guidelines on "Primary prevention of allergic disease through nutritional intervention" were published in "Journal of Allergy and Clinical Immunology in Practice" in 2013.[17] Both of these documents are in keeping with recommendations published in this journal in 2012. This is what we are currently able to recommend to our patients, based on evidence and systematic reviews of methodologically sound studies in the 1990's and first decade of 2000. In brief, such strategies which still "hold" are as follows:

1. MATERNAL DIET DURING PREGNANCY

Unborn children may be sensitised to foods their mothers consume, hence manipulation of maternal diet may influence food sensitisation patterns in the offspring. Studies of allergen avoidance versus consumption during pregnancy have been conflicting. For example, with peanut ingestion during pregnancy, a US study in the consortium of food allergy research noted maternal ingestion of peanut during pregnancy was associated with the infant having increased peanut specific IgE and hence a greater potential towards in peanut allergy.[18] Conversely, a large Danish birth cohort (61 000) of children of mothers with frequent intake of peanut in pregnancy were less likely to have asthma at 18 months.[19]

Overall, systemic reviews and randomised trials, and indeed a Cochrane review from 2012, have found no benefit from restricting common food allergens among pregnant woman. This includes dairy, egg, wheat and peanut.[20]

Our current advice is therefore to consume allergenic foods "as before" in the mother's diet. This is of course very different to recommendations to avoid foods which carry a risk of transmitting infection, such as unpasteurised cheeses or seafood from an irreputable source. Such foods should still be avoided during pregnancy, but not for allergenic reasons.

2. MATERNAL DIETARY SUPPLEMENTATION DURING PREGNANCY

Maternal supplements which may affect maturation of the immune system of the offspring, or affect the microbiota pattern in the offspring, have also been studied in pregnancy.

a. **Maternal fish oil supplements:** Fish oil supplements may show a trend towards reduced sensitisation to allergenic foods such as egg, however, no beneficial effect on the development of food allergy has been demonstrated.[21,22] This may warrant further study but cannot currently be recommended as an allergy prevention strategy.

b. **Maternal probiotic supplementation:** There is currently insufficient evidence for maternal probiotics during pregnancy for food allergy prevention. One good quality trial found a benefit for sensitisation, but was not conclusive for food allergy prevention.[23] Probiotics will be discussed further in the section on infant supplementation.

3. THE VALUE OF BREASTFEEDING

Breastfeeding is widely promoted for its many benefits. Although exclusive breastfeeding for 4-6 months is generally recommended, data for allergy prevention is conflicting.

Several studies have shown at least some benefit from breastfeeding on food allergy and eczema prevention,[24] however, breastfeeding beyond 6 months does not seem to confer additional benefits.[25] Maternal breastfeeding for the first 3 months seems to reduce the incidence of AD,[26] possibly via ingestion of soluble IgA.[27] Randomised studies and a systematic review found a reduction in the incidence of cow's milk protein allergy (CMPA) with exclusive breastfeeding for 4 months compared with feeding with CMP formula, but this cannot be generalised to other food allergies.[28,29] Breastfeeding may also reduce the number of early (mainly viral-related) wheezes.[17,30]

However, the more long-term protective role of breastfeeding is still controversial especially with view to long term benefits in AD and asthma.[17] Disappointingly, some studies have shown that extensive exclusive breastfeeding may increase food sensitisation and allergy in high risk infants, and other studies have shown an increase in AD with breastfeeding amongst children with no parental allergic history.[17,31,32]

In summary, breastfeeding for the first 4-6 months of an infant's life is still recommended as an allergy prevention strategy, but the preventive effect is probably not as large as originally thought. Benefits beyond 6 months are questionable.

4. MATERNAL DIET DURING LACTATION

Mothers may inadvertently sensitise their children to certain foods through breast milk, however, changing maternal diets during breastfeeding have not been found to influence food allergy in the infant.[11]

Therefore, during lactation, maternal avoidance of highly allergenic food is not recommended as an allergy prevention strategy. Note this recommendation does not apply to infants who already show signs of allergic disease from an early age, in whom maternal avoidance of certain foods may form part of the management.

Moreover, maternal probiotics and fish oil supplementation during lactation have not been shown to reduce infant food allergy.[33,34]

5. FORMULA FEEDING

No formula milk has been found to be more beneficial than breastfeeding as an allergy prevention strategy. However, there is evidence to recommend that hypoallergenic hydrolysed cow's milk-based formulas with proven clinical efficacy be used in high risk infants as a primary prevention strategy, for the first 4 months, if breastfeeding is not possible.[16,17] The cost-benefit ratio of use of hydrolysed formula in high risk infants unable to exclusively breast feed has also been found to be favourable.[35]

Several systematic reviews and randomised trials have suggested that extensively hydrolysed whey and casein formula milks may have a protective effect against allergies in comparison to cow's milk formulas.[36] Several trials have also shown that partially hydrolysed formulas may also protect against food allergy in comparison to standard cow's milk formula.[16,17,36,37] Direct comparisons between outcomes with various formulas are difficult due to methodological differences; however it seems that extensively hydrolysed formulas may have a slight edge over partially hydrolysed formulas,[17,38] but come at a much greater financial cost. A meta-analysis found no significant difference between whey and casein based hydrolysed formulae.[39]

The most substantial of the studies on different formula milks, The German Infant Nutritional Intervention (GINI) study (n=2252), compared the preventive effect of 3 hydrolysed formulae versus a standard cow's milk formula as breast milk substitutes in high risk infants.[40] A 10 year follow-up of the GINI study continued to show a reduced cumulative risk of AD (but not food allergy) with a relative risk 0.72 for extensively hydrolysed casein formula and 0.82 for partially hydrolysed whey formula.[41]

In another study of 679 children receiving hydrolysed versus whole cow's milk formula, the group with hydrolysed formula had lower sensitisation to cow's milk protein after 6 months (12.7% v 23.4%, p = 0.048).[42] However, not all studies have mirrored such promising results for allergy reduction with hydrolysed formulas. A study by Lowe et al. showed no differences for eczema, food reactions or

sensitisation using partially hydrolysed whey based formula.[43] The use of hydrolysed formula reduces intake of lactose and oligosaccharide components provided by breast milk, with possible disadvantageous consequences for the development for healthy gut microbiota.[44] There is no evidence for soya-based formulas in allergy protection in comparison to cow's milk based formulas.[45]

6. NUTRITIONAL SUPPLEMENTS IN INFANTS

The role of intestinal microbiota in immunological health has been a topic of recent discussion, and there is evidence that children who develop AD have a reduced diversity in gut microbiota.[46]

Probiotics are supplements containing micro-organisms with the intention of conferring a health benefit to the host, and can be used to alter gut flora. It is still unclear whether probiotics are helpful in AD prevention. Some studies have shown positive findings; a recent meta-analysis of 3 studies looking at probiotics in pregnancy and early life have shown a relative reduction in AD of 21%.[47] However, several randomised trials and systemic reviews have shown no benefit against food allergy or sensitisation.[48,49] The World Allergy Organization published a position paper in 2012 which concluded that probiotics do not yet have an established role in prevention or treatment of allergies.[50] The potential role of prebiotics will be discussed under the "What's New" section.

As far as fish oil supplementation goes, a double blind randomised controlled trial of fish oil amongst 420 high risk infants did not show a protective effect on AD development.[51]

7. INTRODUCTION OF COMPLEMENTARY FOODS (SOLIDS) IN INFANTS

The optimal timing of introduction of solids has been the subject of much debate and recent change. There is a growing body of evidence that excessive avoidance of natural exposure to allergens can lead to impaired immunological tolerance.[52]

Some studies have suggested that introducing solids earlier than 4 months may increase the risk of food sensitisation and eczema,[53] but this in itself is inconclusive.[17] What is more conclusive is that delaying solids beyond 4 months of age does not seem to confer additional allergy protection protective benefits, but may in fact be a risk

**TABLE I: ALLERGY PREVENTION STRATEGIES WHICH ARE CURRENTLY RECOMMENDED**

*Recommendations for all infants:*

- Maternal avoidance of allergenic foods such as egg and dairy is not recommended during pregnancy.
- There is inconclusive evidence for peanut avoidance during pregnancy hence this recommendation cannot be made.
- A generally healthy diet is recommended with as much dietary diversity as possible.
- No special diet is required for the lactating mother (except if the infant is already showing manifestations of particular allergies).
- There is no clear evidence to support the use of supplements such as probiotics, fish oil supplements or vitamin D during pregnancy and lactation.
- Exclusive breastfeeding for 4-6 months is recommended; ideally there should be an overlap between breastfeeding and solids introduction.
- Introduction of complementary foods is recommended between 4-6 months of age according to normal standard weaning practices for all children, irrespective of atopic heredity.
- There is no evidence to delay introduction of allergenic solids such as dairy, wheat, egg and peanut beyond 6 months of age (an exception is the child who is already showing signs of allergies. Such children need a thorough allergy assessment to guide introduction of allergenic solids).
- The infant should have as diverse a diet as possible in the first year of life.

*Additional recommendations for high risk infants (those with a strong family history of atopy):*

- If exclusive breastfeeding is not possible for the first 4 months, a documented hypoallergenic formula is recommended.
- There is no evidence for use of soya milk (or milk of other mammalian origin such as goat's milk) as an allergy prevention strategy.
- There is insufficient evidence to recommend supplementations including probiotics, fish oil or vitamin D to the infant as an allergy prevention strategy.
- Emollient use from an early age may reduce the risk of atopic dermatitis.

factor for food allergy and eczema development.[54,55]

Therefore, the current recommendation of EAACI and AAP is the introduction of complementary foods between 4-6 months according to local standard practice and the needs of the infant, irrespective of atopic heredity. Note that the World Health Organization still recommends exclusive breastfeeding for 6 months, mainly from the point of view of protecting against infectious diseases.

As far as highly allergenic solids go, current studies are showing a trend towards an advantage of earlier introduction. Some studies with retrospective data indicated that introduction of egg between 4 and 6 months may protect against egg allergy.[56] In an Australian cohort of 2589 infants, the delayed introduction of egg after 12 months compared with introduction at 4-6 months showed an increased odds ratio of egg allergy of 3.4 (1.8-6.5).[57] A Finnish study showed that the introduction of fish at 9 months or less also reduced allergic rhinitis and atopic sensitisation.[58] Further studies have shown that earlier wheat introduction before the age of 7 months may be beneficial to reduce wheat allergy.[59] Studies with more rigorous design methodology are currently underway and will be discussed in the "Something New" section below.

In summary, there is no benefit in withholding exposure to potentially allergenic foods once weaning has commenced, irrespective of atopic heredity. *However, if the infant already shows signs of atopy or allergy*, *further evaluations need to be pursued to aid in the prudent introduction of solids.* Furthermore, introducing potential food allergens whilst continuing to breastfeed may provide a reduced risk for development of food allergy.[25]

## "SOMETHING BORROWED"

Before moving on to the "Something New" section, credit must be given to the "borrowed principles" which sparked research into several of the new allergy prevention strategies.

Firstly, came the observation that children in Israel, where consumption of a peanut snack tends to occur from an early age onwards, had a particularly low rate of peanut allergy; incrementally lower than Jewish children in the UK.[15] This was a key driver in the concept that allergen avoidance may not be the best strategy for allergy prevention.

Secondly, we owe a lot to the discovery of the filaggrin gene, which codes for the filaggrin protein, which is involved in maintenance of the skin barrier. Filaggrin gene defects were initially associated with asthma in children with eczema, but more recently also with food sensitisation and allergy risk.[60] These findings sparked the concept of the impaired skin barrier as a potential site of allergen sensitisation, a concept on which many of our newer allergy prevention strategies rely.

Thirdly, studies of high allergy rates in the offspring of migrant populations,[11,61,62] highlighted the risks involved in more westernised lifestyles and the concept of "epigenetic influences" affecting disease expression.

Lastly, the old "hygiene hypothesis"[63] suggesting that certain infectious diseases and "unhygienic" environments may in fact be protective against allergic diseases has given birth to the concept of the importance of microbial diversity in reduction of allergies.

These "borrowed" findings have led to research into the latest findings in the realm of allergy prevention.

## "SOMETHING NEW"

Research and publications on allergy prevention strategies in the past 3-4 years have focused broadly on the following topics, which will be discussed in this section:[64-67]

1. Skin barrier dysfunction as a source of allergic sensitisation.
2. Earlier oral introduction of allergens to induce tolerance.
3. Diversity of maternal and infant diet in allergy prevention.
4. Microbial diversity in the infant.
5. Supplements which have an immunomodulatory effect.
6. Maternal stress and illness affecting allergy in the offspring.

### 1. SKIN BARRIER DYSFUNCTION AS A SOURCE OF ALLERGIC SENSITISATION

Several newly published studies support the notion that epicutaneous exposure (via the skin) to allergens is associated with an increased risk of sensitisation and allergy, especially if there is reduced skin barrier integrity.[64-67] Reduced skin barrier integrity can come about either through established atopic dermatitis, through mutations in the filaggrin gene or through dysfunction in filaggrin protein.[68,69,70,71] Animal models suggest a mechanism whereby skin exposure bypasses oral tolerance, thereby increasing the risk of allergy.[72] Roasted peanut, in particular, may have properties facilitating cutaneous sensitisation.[73] A UK study investigating a pre-birth cohort (n = 623) till the age of 11 years showed that environmental exposure to peanut dust in the absence of other risk factors was not related to outcome, except in those with filaggrin gene defects or eczema, in whom increasing environmental peanut exposure had a dose response increase in peanut sensitisation and allergy at school age.[74,75]

With epicutaneous exposure to allergenic foods being unfavourable for tolerance induction, improvement of the skin barrier has now been adopted as a promising approach to allergy prevention. Two studies have been published in the past year looking at prophylactic emollient use in infants. Simpson et al.[76] looked at 124 neonates at high risk for AD;

the active arm started daily emollients before three weeks of age, and the placebo arm had no emollients applied. The relative risk reduction in AD was 50% in the active group. Horimukai et al.[77] studied 116 neonates, comparing early moisturiser versus no moisturiser, and found a reduced AD prevalence of 40% at week 32 in the active group.

Intensive emollient use in early life as well as avoidance of soap and detergent are being studied as primary prevention strategies in a large scale randomised controlled trial, the BEEP ("barrier enhancement for eczema prevention") study. Others are working on new barrier enhancing preparations to upregulate filaggrin expression.

Other risk factors/strategies being studied in relation to skin barrier dysfunction are the role of pollutants and the role of water softeners.

Air pollutants may act as risk factors for the development or aggravation of AD by inducing oxidative stress in the skin, leading to skin barrier dysfunction or immune dysregulation.[78]

Addition of water softeners in the treatment of AD has not been effective,[79] however, their role in prevention of skin barrier breakdown deserves further research.

## 2. EARLIER ORAL INTRODUCTION OF ALLERGENS TO INDUCE TOLERANCE

Oral ingestion of antigens may result in priming of an effector repertoire, diversification of gut microbiota and immunoregulation driving immune tolerance.[80] We have learned that delaying oral exposure to allergens during a time of environmental skin or respiratory exposure is a risk factor in those with skin barrier defects. What can we do to prevent this? Firstly, enhancement of the skin barrier itself, as described above. Secondly, reducing environmental exposure until oral introduction is possible, may be a potential strategy.[65] Thirdly, finding an "optimal window" for oral introduction of antigens during which the chance of immune tolerance is greatest has been a quest in the past few years. Smaller or retrospective studies suggesting that earlier introduction of allergenic foods such as egg[57,58] may be beneficial have been mentioned under the "What is old but holds" section. Similar findings have been suggested for wheat[59] and milk.[81] Such studies have not been without methodological flaws.

Earlier this year saw the publication of a landmark study on the timing of solids introduction: a randomised control trial on optimal timing of peanut introduction in the infant at risk of peanut allergy (those with eczema or those with egg allergy).[82] Six hundred and forty infants between 4-11 months of age were assigned to consume or avoid peanut until 60 months of age. Amongst the 530 infants who, at study entry, tested negative on peanut skin prick test, the prevalence of peanut allergy at 60 months age was 13.7% in the avoidance group and 1.9% in the consumption group ($p < 0.001$); whilst amongst 98 participants who already had a low positive skin prick test to peanut at study entry, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group ($p = 0.004$). In conclusion, the early introduction of peanut significantly decreased the development of peanut allergy amongst children at high risk for this allergy, and modulated immune response to peanuts.

It seems therefore that we should, using prudent judgement of course in high risk cases, "seize the moment" for solids introduction if a child is not yet significantly sensitised to a food, to try and sway the immune system towards the side of tolerance.

Further larger studies looking into timing of solids introduction are now underway. In the UK, a randomised controlled trial is underway to test introduction of solids at 3 months of age plus concomitant breastfeeding versus exclusive breastfeeding until 6 months (Enquiring about Tolerance or EAT study).

## 3. DIVERSITY OF MATERNAL AND INFANT DIET IN ALLERGY PREVENTION

Several studies have looked into potential benefits of dietary diversity in pregnant women and infants as an allergy prevention strategy. A study researching the association between maternal pregnancy diets to atopy in an unselected cohort of 1277 children, pre-birth to 8 years, showed results as follows: higher maternal first trimester peanut intake was associated with lower peanut allergy, higher milk intake with reduced asthma/rhinitis; and higher wheat intake in second trimester with reduced AD.[83] Other observational studies have suggested that high fish intake in pregnancy lowers AD risk in offspring,[84] and higher maternal intake of dairy products may reduce the risk of AD and asthma.[85]

Several large studies on the effect of infant food diversity on allergies have recently been published. A Finnish study showed that greater food diversity before the age of 12 months was associated with less asthma and AR at 5 years.[86] A European cohort of rural children also found a protective effect of first year food diversity on asthma and food allergy at age 6 years.[87] A UK study using prospective food diaries showed that ongoing higher intake of fruit, vegetables and home-made food was associated with less food allergy by 2 years.[88] Increased food diversity may confer protective benefits by leading to generally healthier diets, earlier introduction of foods and better gut/immunological maturational effects.

## 4. MICROBIAL DIVERSITY IN THE INFANT

Not only food diversity, but microbial diversity also plays a role in immunological maturation and tolerance acquisition. A more diverse intestinal microbiota in the first week

of life has been associated with reduced subsequent onset of eczema in infants at risk of allergic disease.[89] Early interventions to enhance microbial diversity in early life may thus be useful in prevention of eczema and possibly food allergy in high risk infants.

The use of probiotics in pregnancy and infancy is still controversial as an allergy prevention strategy. This has been discussed in the "What is old but still holds" section. The WAO position paper still cautions that further research into probiotics is needed before a firm recommendation can be made.[50]

Perhaps more specific bacteria need to be targeted when looking at microbial diversity. Colonisation with intestinal clostridia in first 3 months of life has been associated with increased AD whilst acinetobacter species in the skin protect against inflammation.[90]

Prebiotics have perhaps shown greater potential in the past few years. Prebiotics (such as fructo- and galacto-oligosaccharides) are food components that are suitable substrates for non-pathogenic bacteria, promoting their growth and activity. Breastmilk is the prototype food for containing beneficial prebiotics. Studies have shown that supplementation with prebiotics and oligosaccharides may reduce the occurrence of AD, with similar results as compared with breastfed babies.[91] A recent Cochrane review of prebiotic use in the postnatal period suggested a reduction in risk of AD of around 30% by 2 years age.[92]

Other "sources" of microbial diversity have been suggested, for example, unpasteurised milk and environmental "dirt". A Polish study showed that the consumption of unpasteurised milk in the first year of life was inversely associated with atopy (by skin prick tests) and asthma: in town-dwelling patients, adjusted odds ratio was 0.46 for atopy and 0.51 for asthma.[93] House dust mite reduction strategies have not been shown to reduce AD; conversely, there is evidence that high environmental house dust mite in early life reduce AD risk.[94]

5. SUPPLEMENTS WHICH HAVE AN IMMUNOMODULATORY EFFECT

Vitamin D has been shown to have an immunomodulatory effect, reducing allergic inflammation, and improving skin barrier function.[95] A recent study has shown that winter-related AD can be improved with Vitamin D supplementation.[96] This has sparked great interest in the role of Vitamin D in pregnancy and infancy as a prevention strategy for AD. Vitamin D is still controversial in pregnancy: a deficiency has been associated with asthma and AD in the offspring,[97] but in other studies Vitamin D supplementation has been shown to increase the risk of infantile eczema.[98] In conclusion, there is currently no evidence that vitamin D supplementation is an efficacious method to prevent AD.[99]

6. MATERNAL STRESS AND ILLNESS AFFECTING ALLERGY IN THE OFFSPRING

Abnormal immune development in response to adverse intrauterine exposures might increase the risk of asthma and atopic disorders in childhood via an intrauterine programming effect. Maternal psychological distress is one such exposure that could lead to developmental adaptations of the hypothalamic-pituitary-adrenal axis, autonomic nervous system, lung structure and immune response in the offspring. A population based study from the Netherlands found that children exposed to maternal psychological distress during pregnancy had increased odds of childhood wheezing until 4 years of age.[100]

Another large study of 1587 mothers researched the association between common life stressors (job loss, residential move, economic or marital problems) in pregnancy and atopic disease at ages 6 and 14 years.[101] This study found that asthma at ages 6 and 14 years, as well as eczema at 14 years, were significantly associated with prenatal maternal life events between 18-34 weeks gestation. Thus prenatal events seem to increase the risk of manifest (persistent) atopic diseases in children.

## CONCLUSION

The significant burden of allergic disease worldwide and lack of a cure for allergies make prevention an attractive strategy. Progress has been made in the past decade which can now promote maintenance of skin barrier integrity via prophylactic emollients, enhancement of infant gut microbial health, perhaps via breastfeeding and prebiotics, promoting oral tolerance by timing oral introduction of allergenic solids far earlier than previously suggested, encouraging dietary diversity in pregnant mothers as well as infants, and avoiding excessive psychological stresses during pregnancy.

Some of these strategies, especially those relating to the timing of introduction of allergenic solids, will require a "paradigm shift" away from the previously entrenched message of allergen avoidance.[102]

A greater understanding of the drivers behind the increase in allergies over the past few decades will help direct further prevention strategies.

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