

REVIEW

Allergy Prevention: An Overview of Current Evidence

Candice Royal* and Claudia Gray

Paediatric Allergology, Kidsallergy Paediatric and Allergy Centre, Cape Town, South Africa

Background: There has been a rapid rise in allergic disorders across the globe. This has increased research into the determinants of allergy development, to identify factors that may be manipulated to mitigate risk. An opportune window in immunological development appears to exist in early life whereby certain exposures may promote or prevent the development of an allergic disposition. Furthermore, factors that affect the composition and diversity of the microbiome in early life have been explored. In this review, we discuss current literature and recommendations relating to exposures that may prevent allergy development or promote tolerance. **Risk factors and recommendations:** Delivery by caesarean section, omission of breastfeeding, vitamin D insufficiency, and environmental exposures, such as cigarette smoke exposure, all increase the risk of an allergic predisposition. Dietary diversity during pregnancy, lactation, and in infancy is protective. Breastfeeding for at least 4 months reduces the risk of eczema. Recommendations for food-allergen exposure has shifted from delayed introduction to early introduction as a tolerance-inducing strategy. Supplements such as probiotics and vitamins during pregnancy and infancy have yet to produce conclusive results for allergy prevention. Emollient use in infancy has not been shown to be protective against eczema or food allergy.

INTRODUCTION

An allergy is an inappropriately “overactive” immune response to antigens that may result in the development of the allergic disorders such as atopic dermatitis, allergic rhinitis, asthma, and food allergy. Allergic disorders have increased in prevalence over the last few decades. The initial rapid rise in respiratory allergy, first seen in developed countries and subsequently in the developing world, has been followed by a significant increase in the

prevalence of atopic dermatitis and food allergy. Allergic conditions remain a cause of significant morbidity and healthcare expenditure and, while manageable with chronic treatment, to a large degree have no cure. With this in mind, research on allergy prevention has received much attention [1-6]. Increased understanding of the fetal and early life influences in the development of allergy have fueled interest in the possibility of a “window” in which primary prevention strategies might be utilized to abort allergy development.

*To whom all correspondence should be addressed: Candice Royal, Paediatric Allergology, Kidsallergy Paediatric and Allergy Centre, Cape Town, South Africa; Email: candice@kidsallergy.co.za.

Abbreviations: AD, atopic dermatitis; n3-PUFAs, Omega-3 polyunsaturated fatty acids; SCFA, short chain fatty acids; WAO, World Allergy Organization; CMPA, cow’s milk protein allergy; pHF, partially hydrolyzed formula; eHF, extensively hydrolyzed formula; OFC, oral food challenge; SCORAD, scoring atopic dermatitis.

Keywords: allergy, prevention

EARLY LIFE INFLUENCES ON THE DEVELOPMENT OF ALLERGY

Pregnancy is essentially a T helper type 2 (Th2) lymphocyte-dominant regulatory environment, in order to counteract the potentially harmful maternal Th1 response against feto-paternal antigens [7]. The cytokine milieu of the fetus is thus dominated by IL-4, IL-5, and IL-13. Following birth, the Th2 skewed response needs to switch to a more balanced Th1/Th2 milieu to prevent immunological swaying towards allergies and improve anti-infective responses. Factors which are key to this switching process are genetics, timing, and quantity of allergen exposure and environmental exposures.

GENETIC INFLUENCES

There is extensive evidence that genetics play an important role in allergy causation. This occurs through two different mechanisms. Firstly, this may be directly through a specific genetic polymorphism which results in diseases associated with allergy, for example, CARD11 polymorphism which results in eczema. The second mechanism is through the process of epigenetics whereby environmental factors (including nutrition, lifestyle factors, pollution, intrauterine environment) change the way in which genes are *expressed*, without directly changing the gene DNA sequence [8]. These changes may manifest in allergic conditions dependent on allergen exposure and environmental influences [9]. Epigenetic changes are critical in early life to influence immune programming and affect the expression of disease. Epigenetic changes may be heritable, resulting in an altered phenotype in the offspring.

The rapid rise in allergies throughout the globe cannot be explained by specific mutations in genetics alone. Rather, this complex interaction between genetics and environmental factors in early life is at the heart of the allergy epidemic. Exploring environmental causes for epigenetic change represents a key area for possible primary prevention of allergy. This includes timing of exposure to environmental and dietary allergens.

Epigenetic influences are well 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, the children of these immigrants have a higher allergy prevalence matching or even exceeding that of the local population [10].

THE MICROBIOME

The role of the human microbiome is another key area of allergy research. The microbiome is an ecological

community of micro-organisms that can be found on all multicellular organisms. The microbiome of the gut and skin has significant interaction with the immune system and influences its function. Depletion of the variety of species comprising the microbiome may lead to an immunological sway toward an allergic predisposition [11]. Greater understanding of the components of a healthy microbiome and the factors that lead to its depletion is an area of great interest for the prevention of allergy at all levels.

PREVENTION OF FOOD ALLERGY AND ECZEMA

Food allergy and atopic dermatitis (AD) impose a significant reduction in quality of life and increase in burden on the healthcare system. The global prevalence of AD ranges from 0.2% to 24.6% and up to 8% of individuals have food allergy [12]. Allergy prevention strategies are targeted to the “window of opportunity” largely completed by 2 years of age.

Maternal Diet During Pregnancy

Several studies have sought to distill associations between maternal diet and allergic outcomes in their children, however, these are mostly observational and offer conflicting outcomes. Studies that have examined total maternal diet include those exploring a “healthy eating diet” (the definition thereof varied between studies) and a typical “Western” diet have produced inconsistent findings. Adherence to a Mediterranean diet may be beneficial but further interventional studies are required [13].

Systematic reviews and randomized trials have been conducted to evaluate the effects of maternal consumption of specific common allergenic foods during pregnancy. Notably, a Cochrane review from 2012, found no benefit from restricting common food allergens among pregnant women [14]. This includes dairy, egg, wheat, and peanut. Furthermore, it was concluded that dietary interventions during pregnancy may compromise maternal and fetal health.

Enhanced dietary diversity of fruit and vegetables has been associated with reduced risk of allergic outcomes. Higher maternal intake of green and yellow vegetables and citrus fruit was associated with reduced infantile eczema [15]. Observational studies have suggested that maternal fish consumption during pregnancy is protective for allergy outcomes in their offspring, however, a systematic review in 2017 failed to validate this association [16,17]. Higher maternal intake of dairy products may reduce the risk of atopic dermatitis and asthma [18]. In summary, international advisory bodies including the European Academy of Allergy and Clinical Immunology

gy (EAACI) and the American Academy of Pediatrics (AAP) recommend dietary diversity and advise against allergen avoidance during pregnancy.

Maternal Dietary Supplementation During Pregnancy

Maternal supplements may affect maturation of the immune system of the offspring or affect the microbiota pattern in the offspring. Omega-3 polyunsaturated fatty acids (n3-PUFAs) supplementation during pregnancy has been considered as a mechanism of reducing the risk of allergic disorders. A Cochrane review in 2015 concluded that there was no significant difference between children of those who were supplemented with n3-PUFAs and those who were not. A meta-analysis in 2016 including additional trials suggested there may be some benefit, however, this could not be confirmed due to inconsistencies in the results. At present there is thus insufficient data to recommend supplementation [19-21].

Vitamin D has been shown to have an immunomodulatory effect, reducing allergic inflammation, and improving skin barrier function. Currently there is insufficient evidence to support the use of supplemental vitamin D to prevent food allergy and eczema [13].

The ability to positively affect the newborn gut microbiome is an area of much interest. Prebiotics (such as fructo- and galacto-oligosaccharides) are food components that are suitable substrates for non-pathogenic microbes, promoting their growth and activity. Additionally, gut micro-organisms ferment prebiotics to produce short chain fatty acids (SCFA) that have an anti-inflammatory effect on the gut and improve intestinal integrity. At present, there is insufficient evidence to recommend maternal supplementation with prebiotics to prevent the development of eczema and food allergy. Randomized controlled trials, such as the SYMBA and PREGALL studies, are in progress and will hopefully add evidence to guide further recommendations [22].

Probiotics are supplements containing microorganisms with the intention of conferring a health benefit to the host and can be used to alter gut flora. Prenatal administration of probiotics has been demonstrated to have some protective effect for the development of infantile eczema and is currently recommended by the World Allergy Organization (WAO) for high-risk offspring. Further data regarding optimal probiotic strain for supplementation and the timing and duration thereof is needed [23].

Mode of Delivery

Delivery by caesarean section is associated with a higher prevalence of atopic disorders in childhood [24]. This may be related to alterations in the initial colonization of the infant's microbiome [25].

The Value of Breastfeeding

Breastfeeding is widely promoted for its many benefits and contains a vast array of bioactive factors including growth factors, neuropeptides, anti-inflammatory, and immunomodulatory agents that influence many physiological systems and promote normal gut colonization. Although exclusive breastfeeding for 4-6 months is recommended, the preventive effect is probably not as large as originally thought. Benefits beyond 6 months are questionable [26,27]. Randomized 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 generalized to other food allergies [28].

Maternal Diet During Lactation

Mothers may inadvertently sensitize their children to certain foods through breast milk; however, changing maternal diets during breastfeeding have not been found to influence food allergy or other allergic outcomes in the infant. Studies exploring the association between maternal avoidance diets and allergy in their infants have been contradictory and thus maternal avoidance of highly allergenic food is not recommended as an allergy prevention strategy [29]. 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.

Supplementation of the maternal diet during lactation has yielded similar conflicting results as those examining association with supplementation in pregnancy. At present there is no clear evidence to advise supplementation with n3-PUFAs, vitamin D, prebiotics, or probiotics.

Formula Feeding

Formula milk is not more beneficial than breastfeeding as an allergy prevention strategy. When breastfeeding is not possible, allergy prevention strategies have previously recommended that hypoallergenic hydrolyzed cow's milk-based formulas be used in high risk infants as a primary prevention strategy for the development of allergic outcomes [3,4]. Current literature does not support the use of partially or extensively hydrolyzed formulas. See Table 1.

Many international societies are revising their recommendations and no longer recommend a partially hydrolyzed formula (pHF) or extensively hydrolyzed formula (eHF) over a conventional cow's milk-based formula. Amino acid-based formulas have not yet been studied in the primary prevention of allergy. There is no evidence for soy-based formulas in allergy protection although these remains an important component of treatment of some types of cow's milk protein allergy [34].

Table 1. A summary of available data on the use of partially and extensively hydrolyzed formula to prevent allergic disease.

Author	Study Objective	Outcome
Von Berg <i>et al.</i> [30] GINI*	Comparison of the preventative effect of three hydrolyzed formulas with standard cow's milk formula	10- and 15-year follow-up showed reduced risk of AD, particularly with extensively hydrolyzed casein formula
Boyle <i>et al.</i> [31]	Systematic Review and meta-analysis of the preventative effect of hydrolyzed formula for the development of allergic disease	No evidence that partly or extensively hydrolyzed formula affected the outcome of allergic disease
Szajewska <i>et al.</i> [32]	A meta-analysis comparing pHW-F** with standard cow's milk formula and allergic outcomes	Decreased risk of eczema in high-risk infants at certain ages who consumed partially hydrolyzed whey formulas
Osborn <i>et al.</i> [33]	A meta-analysis comparing pHW-F with standard cow's milk formula	No reduction in infantile allergic disease

*German Infant Nutritional Intervention; **pHW-F partially hydrolyzed formula

Nutritional Supplements in Infants

Intestinal microbiota play an important role in immunological health, and there is evidence that children who develop AD have a reduced diversity in gut microbiota. Early interventions to enhance microbial diversity in early life may thus theoretically be useful in prevention of eczema and possibly food allergy in high risk infants. A Cochrane review of prebiotic use in the postnatal period suggested a reduction in risk of AD of around 30% by 2 years age [35]. More research is needed to optimize the usage of prebiotics in preventing allergic diseases and at present is only recommended by the WAO for high-risk infants to reduce infantile AD [22]. It is still unclear whether probiotics are helpful in AD prevention as studies have produced conflicting results [36-40].

Fish oil supplementation was not found to have a protective effect for the development of AD in a double blind randomized controlled trial of fish oil amongst 420 high risk infants [41]. There is also insufficient evidence that vitamin D supplementation in the infant has a protective effect. Optimal vitamin D levels for "immunological health" still need to be established. The VITALITY trial is currently underway and is the first randomized control trial to evaluate the efficacy of vitamin D supplementation in infancy to prevent food allergy. It is anticipated that the results of this study will guide recommendations with respect to routine vitamin D supplementation in infancy [42].

Introduction of Complementary Foods (Solids) in Infants

Oral ingestion of antigens results in immunoregulation driving immune tolerance. Cutaneous antigen exposure (for example, via a defective skin barrier in atopic dermatitis) predisposes towards a T helper 2 skewed

environment, which may lead to allergic sensitization. Potential allergy prevention strategies include finding an "optimal window" for oral introduction of antigens during which the chance of immune tolerance is greatest. This is supported by a growing body of evidence that excessive avoidance of natural exposure to allergens, the previous strategy of food allergy prevention, can lead to impaired immunological tolerance [43]. Current evidence suggests that delaying solids beyond 4 months of age does not confer additional allergy protective benefits. The converse appears to be true, delayed introduction may in fact be a risk factor for allergy development [44,45].

Infants with a first-degree relative with atopy and those with AD are considered to be high-risk for the development of allergic disorders including food allergy. In this group specifically, delayed introduction of highly allergenic groups may increase the risk of allergy, whereas early introduction, between 4 and 6 months, may be protective against development of allergy to that specific dietary allergen [46,47].

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. The World Health Organization still recommends exclusive breastfeeding for 6 months as a public health measure to reduce infectious diseases in infancy.

Highly allergenic foods include egg, peanut, tree nuts, cow's milk, soy, wheat, fish, and shellfish; however, this may vary according to population-specific dietary practices. Observational studies exploring timing of introduction of highly allergenic solids have trended towards an advantage of earlier introduction, however, these are not without methodological flaws including reverse causation [48-50]. Studies with more rigorous design are discussed below.

The **LEAP study (Learning Early About Peanut)** was the first randomized trial to show benefit of early introduction of a highly allergenic food in high-risk infants. The study demonstrated that in high-risk infants, sustained peanut consumption initiated in the first 11 months of life resulted in substantial reduction in the proportion of children with peanut allergy at 60 months of age compared with children who avoided peanut [46]. A reduction in peanut allergy was seen for both infants with negative peanut skin prick test (SPT) response and those with peanut SPT diameters 1–4 mm (minimally positive) at study entry, thus representing both primary and secondary prevention. In the **LEAP-On** extension of the study, benefits on allergy protection in the early consumption group were sustained after 12 months of peanut avoidance [47].

There is now scientific evidence that healthcare providers should recommend introducing peanut-containing products into the diets of high risk infants (those with eczema or/and egg allergy) early on in life (between 4 and 11 months), because delaying the introduction of peanut may be associated with an increased risk of developing peanut allergy. Ideally, at-risk infants would benefit from evaluation by an allergist or physician trained in management of allergic diseases to diagnose any food allergies and assess the appropriateness of early peanut introduction. Evaluation of such patients may consist of performing peanut skin prick tests and/or observed peanut ingestion.

Three clinical trials have assessed the effects of egg introduction in an *at-risk* population group:

In the **PETIT (Prevention of Egg Allergy with Tiny Amount Intake)** trial, 147 infants with eczema and no prior ingestion of egg were randomly assigned to daily consumption of heated egg powder or placebo along with aggressive treatment of eczema. An oral food challenge (OFC) to egg was conducted at 12 months of age. The trial was ended early due to demonstration of a protective effect in the treatment group. It must be noted, however, that both higher SCORAD (scoring atopic dermatitis) scores and specific IgE levels to egg were present at baseline in the placebo group [51].

The second trial, **STEP (Starting Time of Egg Protein)**, enrolled a group of infants determined to be high-risk due to a maternal allergic disease but without eczema, and assigned them to either ingestion of raw whole-egg protein or placebo. OFC at 12 months did not show significant difference in the presence of egg allergy between the two groups [52].

Finally, the **BEAT (Beating Egg Allergy Trial)** enrolled 319 infants with a first degree relative with an allergic disorder but a negative SPT to egg and assigned them to either daily ingestion of raw whole-egg protein from 4 months of age or placebo. There was significant loss to follow-up with only 254 participants having at least

partial assessment at 12 months. Notably 14 infants in the treatment group were lost to follow-up as they reacted to the egg powder at initiation of treatment. Although there was significantly reduced sensitization to egg in the treatment group, there was no difference in probable egg allergy [53].

Studies that looked at infants recruited from the general population are discussed below:

The **EAT study (Enquiring About Tolerance)** was designed to assess whether early introduction of food allergens would prevent the development of food allergy in infants recruited from the general population [54]. Infants who were exclusively breastfed at 3 months of age were randomly assigned to either early introduction group (introducing peanut, cooked egg, cow's milk, sesame, white fish, and wheat at an early age) or a standard introduction group. The primary outcome was the proportion of children with food allergy to 1 or more of the 6 intervention foods by 36 months of age. In the per-protocol analysis there was a significant reduction in egg and peanut allergy in the early intervention group; this was not statistically significant in the intention-to-treat population though. Modelling determined that 2 or more grams of peanut and egg white protein per week could have an effect in preventing peanut or egg allergy, respectively.

The **HEAP (Hens Egg Allergy Prevention)** trial assigned normal-risk infants to consumption of increasing doses of raw, pasteurized egg or placebo from 4–6 months. The trial showed no statistical difference in egg allergy confirmed by OFC at 12 months. Notably there was a high rate of anaphylaxis at initiation in the treatment group, which may be partially attributed to the raw pasteurized form and the relatively larger amounts of egg protein consumed compared with other early egg introduction randomized, controlled trials [55]. A subsequent meta-analysis combined data on trials of early introduction of egg or peanut in both high-risk infants and the general population found that early introduction of egg or peanut was associated with a decreased risk of allergy to that specific dietary allergen [56].

In summary, there is no benefit in withholding exposure to potentially allergenic foods (specifically peanut and egg) 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.

Diversity of the Infant's Diet

Increased food diversity may confer protective benefits by leading to generally healthier diets, earlier introduction of foods and better gut/immunological maturational effects. Anti-oxidants found in fresh fruits and vegetables may also be beneficial. A UK study using prospective food diaries showed that ongoing higher intake

Table 2. A summary of available data regarding prophylactic emollient use to prevent atopic dermatitis.

Author	Study Objectives	Outcomes
Simpson <i>et al.</i> [58]	High risk newborns assigned to placebo or emollient use	Relative risk reduction in AD of 50% in the treatment group
Horimukai <i>et al.</i> [59]	Emollient use in the newborn period versus no emollient use	Emollient group had a 40% reduced prevalence of AD
Chalmers <i>et al.</i> : BEEP trial [60]	RCT: infants randomized to emollient use or standard skin care	Age 2 years there was no difference in AD in the past 12 months
Skjerven <i>et al.</i> : PreventADALL [61]	RCT: infants randomized into a no intervention group, emollient use only, early introduction of foods group and a emollient and food intervention group	The rate of atopic dermatitis at 12 months was similar in all groups

of fruit, vegetables, and home-made food was associated with less food allergy by 2 years [57].

Skin Barrier Enhancement

Prophylactic use of emollients in the newborn period has been studied as a preventative strategy. Table 2 summarizes available data. Initially two small intervention studies looking at prophylactic emollient use in infants showed promising results. However, two larger randomized trials (BEEP and PreventADALL) failed to prove benefit. It must be noted that different emollients were used in these clinical trials. It is postulated that newer, improved emollients may have a protective effect on the newborn skin when used in conjunction with other skin care measures [60]. At present there is no convincing data to support the prophylactic use of emollients in the newborn period.

Environmental Exposures in Infancy

A secondary cohort analysis of infants enrolled in the EAT study revealed a 90% reduction in the odds of having a food allergy in infants who lived with dogs. Interestingly, none of the infants who owned more than one dog developed food allergy and a dose-dependent relationship has been postulated. This preventative effect was not found in relation to the development of AD [62].

RESPIRATORY ALLERGY PREVENTION

Genetic, immunological, and environmental factors have complex interactions that affect the respiratory tract and are key to asthma pathogenesis. Diversity of the microbiome may be necessary for a well-balanced immune system and regulated inflammatory responses to inhaled environmental elements such as allergens, particles, and viruses. In early life, complex interactions occur between viral and/or bacterial respiratory infections and aeroal-

lergen sensitization in genetically susceptible subjects triggering immune responses and airway inflammation characteristic of asthma. Such a multifaceted causation makes asthma prevention difficult. Factors which play a role in asthma prevention are summarized below [63]:

Effect of Environmental Exposures

There is no clear evidence that preventive strategies based on reducing indoor allergen exposure are effective. Multi-faceted interventions (environment and diet) may be effective in preventing asthma but need further study. Prenatal and passive tobacco smoke exposure is a well-established risk factor in the development of asthma [64,65].

Nutritional and Microbial Factors

There is no specific dietary avoidance advice during pregnancy and lactation. In fact, a more diverse maternal and infant diet has the potential to be protective against asthma. Observational studies have linked maternal vitamin D deficiency with an increased risk of asthma in their offspring. Maternal supplementation with vitamin D has been examined and a recent meta-analysis of two randomized control trials found a significant reduction in asthma/ recurrent wheeze in the offspring of mothers who received vitamin D supplementation [66]. There is no conclusive evidence for cow's milk protein hydrolysates or delayed introduction of solids beyond 4 months in asthma prevention.

Microbial diversity is protective against asthma. Farm life leads to an overall 25% reduction in asthma, possibly due to microbial exposures and/or consumption of unpasteurized cow's milk [67]. Caesarean sections result in altered infant colonization. Caesarean section delivery is associated with a higher asthma risk in genetically predisposed infants. This association seems to be stronger in emergency caesareans [68]. Maternal antibi-

Table 3. Summary of allergy prevention strategies.

- Maternal avoidance of allergenic foods such as egg, peanut and dairy is not recommended during pregnancy or lactation.
- A generally healthy diet is recommended during pregnancy and lactation with as much dietary diversity as possible and inclusive of a variety of fruit and vegetables.
- 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 for its general beneficial properties; however its role in the protection against food allergy risk remains unclear. Ideally there should be an overlap between breastfeeding and solids introduction.
- There is insufficient evidence that partially or extensively hydrolyzed formulas provide protection against food allergy or eczema.
- 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 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).
- There is evidence that earlier introduction of peanut in high risk patients can reduce peanut allergy.
- The infant should have as diverse a diet as possible in the first year of life.
- There is insufficient evidence to recommend supplementations including probiotics, fish oil, or vitamin D to the infant as an allergy prevention strategy.
- Living with dogs in infancy is associated with a reduction in food allergy.
- Prenatal and passive exposure to tobacco smoke is an important risk factor in the development of asthma and should be strongly discouraged.
- Avoidance of excessive maternal antibiotics during the latter half of pregnancy and in infancy may be protective against development of asthma.
- Excessive maternal psychological stress during pregnancy should be avoided.

otics during pregnancy and excessive infantile antibiotics in the first year of life may increase the risk of asthma. Currently, probiotics have not been shown to have a benefit in preventing asthma or allergic rhinitis.

Pharmacotherapy and Immunotherapy

All drugs studied thus far for primary and secondary prevention of asthma; including antihistamines, nasal corticosteroids, and inhaled corticosteroids, have failed to show conclusive benefit for asthma prevention. However, they may reduce symptoms if allergic rhinitis or asthma are already established. Allergen immunotherapy remains a candidate for primary and secondary prevention of asthma. However, the recent GAP trial (Grazax Asthma Prevention trial) failed to show that grass immunotherapy in children with allergic rhinitis prevents asthma. The trial did show a disease modifying effect in reducing asthma symptoms and medication use [69].

Other Factors Associated with Asthma Development

Major stress or depression during pregnancy has been associated with an increase in asthma in the offspring. Maternal psychological distress could lead to developmental adaptations of the hypothalamic-pituitary-adrenal axis, autonomic nervous system, lung structure, and immune response in the offspring [70].

CONCLUSION

Review of current literature supports the proposition that certain environmental influences may sway the immune system toward allergy in genetically-susceptible individuals. Similarly, other exposures may induce tolerance in the developing immune system. A critical “window of opportunity” exists *in utero*, extending to approximately 2 years of age. Conflicting data from various studies emphasize the complexity and multiplicity of these interactions. The microbiome, furthermore, has become a focus as its ongoing influence on the immune system is increasingly appreciated. Factors that have been established to be protective include normal vaginal delivery, exposure to farm animals and dog-ownership, breastfeeding until at least 4 months of age, early introduction of peanut, and a diverse diet without allergen avoidance during pregnancy, lactation and infancy. Maternal supplementation with vitamin D reduces asthma in the offspring. Supplementation with vitamin D, n3-PUFAs and the use of pre- and probiotics in pregnancy, lactation, or childhood has insufficient evidence to support recommending their use to prevent eczema and food allergy. The use of hydrolyzed cow’s milk formulas and emollients have not been shown to prevent the development of allergic disease. Cigarette smoking is an important risk factor for asthma in the offspring.

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