Guidelines for Allergy Prevention in Hong Kong

Dr. Alson WM CHAN[1*], Ms. June KC CHAN[2], Dr. TH LEE[3]

Prof. TF LEUNG[4], Dr. Alfred YC TAM[5]

On behalf of the Hong Kong Institute of Allergy

1. *Specialist in Paediatrics, Clinical Assistant Professor (Hon.), University of Hong Kong*

2. *Senior Dietitian, Allergy Centre, Hong Kong Sanatorium & Hospital*

3. *Director, Allergy Centre, Hong Kong Sanatorium and Hospital, Clinical Professor (Hon.), University of Hong Kong*

4. *Professor and Chairman, Department of Paediatrics, The Chinese University of Hong Kong*

5. *Specialist in Paediatrics, Clinical Associate Professor (Hon.), University of Hong Kong*

(In alphabetical order by author's last name)

*For correspondence

Dr. Alson WM Chan

Email: awmc@hku.hk

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Declarations of Interest

Dr. Alson WM Chan:
Council Member, Hong Kong Society for Paediatric Immunology, Allergy & Infectious Diseases; Honorary Advisor, Hong Kong Allergy Association.

Ms. June KC Chan:
None declared.

Dr. TH Lee:
President, Hong Kong Institute of Allergy; Convenor, The Hong Kong Allergy Alliance; Honorary Advisor, Hong Kong Allergy Association.

Prof. TF Leung:
Secretary General, Asia Pacific Association of Pediatric Allergy, Respirology & Immunology; Vice President, Hong Kong Society for Paediatric Immunology, Allergy & Infectious Diseases; Honorary Advisor, Hong Kong Allergy Association.
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Dr. Alfred YC Tam:
Honorary Council Member, Hong Kong Society of Paediatric Respirology & Allergy; Honorary Advisor, Hong Kong Allergy Association.

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Executive Summary

Allergic diseases are worldwide health problems. In Hong Kong, about one third of children aged 6-7 years old suffered from rhinitis. One-tenth of secondary school children had asthma and 15% of them had atopic dermatitis. For adverse food reaction, the self-reported prevalence was 8.1%, most commonly caused by shellfish, followed by egg, peanut, cow's milk, beef, tree nuts and fish. The incidence rates of allergies have been increasing in many developed countries.

It is universally recommended that all mothers should include a healthy diet without restriction during pregnancy and lactation. Prophylactic dietary restriction is unlikely to reduce the risk of atopic diseases. Moreover, it may have adverse effects on maternal or fetal nutrition. Breastfeeding is the best source of nutrition in the first 6 months of life for all infants. For high risk infants who could not be exclusively breastfed in the first 6 months, the incidence of atopic eczema was significantly reduced in those consuming extensive and partially hydrolyzed formula, when compared to standard cow's milk formula. Introduction of complementary food is recommended for infants over 4 months of age if they are developmentally ready. Emerging evidence is suggesting that a delay in solid food introduction beyond 6 months, especially with potent food allergens, may increase the risk of food allergy or eczema. The use of probiotics and prebiotics during pregnancy and early infancy are still controversial.

Recent evidence suggests a strong epidemiological association between traffic air

pollution and allergic diseases like asthma, allergic rhinitis and eczema. Active or passive smoking is a significant risk factor for allergic diseases and the effect is more obvious in children and adolescents. Meta-analyses have shown that indoor environments such as home dampness and visible mold are associated with recurrent wheeze and asthma in young children. Exposure to house dust mite is a possible cause of asthma.

There is a clear dose-response relationship between body mass index and the risk of asthma and eczema. A healthy lifestyle should be encouraged to avoid overweight and obesity. A growing number of studies indicate that stressful life events either during pregnancy or in early childhood increase the risk of subsequent atopic diseases. No convincing relationship was demonstrated between the use of pharmaceuticals and atopic diseases. Children should receive vaccinations as recommended including those in the high risk group for developing allergic diseases. Recent evidence has shown that immunotherapy can reduce new sensitizations and prevent the progression from allergic rhinitis to asthma.

The recommendations derived from this guideline are summarized in the table of allergy prevention measures. [Appendix I]

Introduction

In the last 50 years there is a continuous rise in the prevalence of allergic diseases in both developed and developing countries. The situation is especially dramatic in children who are the major group responsible for the rising trend in the last 20 years. Up to 40-50% of school children nowadays are sensitized to one or more common allergens. The growing burden of allergic diseases has been recognized as a new pandemic in the 21st century [1].

It has long been recognized that genetically predisposed children usually develop various allergic diseases in the typical evolution described as 'Allergic March' [2]. Cow's milk and food are the first allergens that infants encountered soon after birth. Their allergies then progress from gut and skin to respiratory tract when they grow older and contact with more environmental allergens [3]. Prevention strategies applied during infancy or early childhood have been shown to stop the manifestations of allergy and its 'marching' from gut to skin and to the airway [4].

However, the dramatic rise in the prevalence of allergic diseases still continues despite efforts on allergen avoidance and delaying the introduction of common food allergens [5]. In contrast over the last few decades, more and more studies have shown that the induction of immune tolerance is the most important

key to success in allergy prevention. Instead of delaying the introduction of certain food, the approach of early food allergen introduction between 4-6 months leads to better immune tolerance and decreasing atopic tendency in the long run [6]. Recent results from the randomized trial of peanut consumption in at risk infants provide translational insight into the induction of food tolerance [7].

In addition new evidence is showing the association of allergy with environmental factors including air pollution and indoor air quality; lifestyle factors such as overweight, sedentary lifestyle and psychological factors. The use of new pharmaceutics and probiotics has also been the new area of debate and discussions.

As the burden of allergic diseases has been increasing rapidly worldwide and in our locality, and the concept of allergy has been changing quickly in the past few years, there is a need to develop an updated guideline in allergy prevention to promote the implementation of evidence based strategies in this area in response to the challenge of this new pandemic of our century.

Epidemiology of Allergic Diseases in Hong Kong Children

Allergic diseases constitute a major health problem worldwide, with asthma being one of the commonest chronic diseases in children. Genetically predisposed children typically acquire different allergic diseases in an "allergy march", which is explained by the order of exposure to different environmental antigens in these subjects. The population-based International Study of Allergies and Asthma in Childhood [ISAAC] identified that about one-tenth of our secondary schoolchildren had asthma and 15% of them had atopic dermatitis. About one-third of Hong Kong children aged 6-7 years suffered from rhinitis [8,9]. The Phase 2 ISAAC confirmed aeroallergen sensitization as a major risk factor for childhood allergies [10], but this relationship varied substantially among populations and increased with economic development [11]. Genetic susceptibility is another major determinant for childhood asthma, and a number of predisposition genes have been reported for childhood asthma and eczema in Chinese [12].

There is limited data on the prevalence and risk factors for atopic disorders among Asian preschool children. Using an ISAAC-based questionnaire, our group reported the prevalence of 'ever' and 'current' wheeze among Hong Kong children aged 2-6 years to be 16.7% and 9.3%, respectively [13]. Consistent with our earlier report for older Chinese children [14], the use of foam pillow and gas as cooking fuel in infancy were significant risk factors for current wheeze in these young children. Interestingly, we found that current wheeze was less common in children born in mainland China and

migrated subsequently to Hong Kong as compared with those locally born and raised. This observation highlighted the importance of early-life environmental exposure as a major determinant of childhood wheezing illnesses.

The incidence rates of asthma and allergies have been increasing in many developed countries. Regarding the trend of allergies, our Phase 3 ISAAC found reduced asthma prevalence over an 8-year period among Hong Kong secondary schoolchildren [15]. The prevalence of asthma ever, wheeze ever and current wheeze was also similar in local children aged 6-7 years between 1995 and 2001, although there was significant increase in life-time and current rhinitis, current rhinoconjunctivitis and life-time eczema during this period [16]. In Thailand, Trakultivakorn et al. compared Phases1 and 3 ISAAC data and reported an increase in the prevalence of current asthma, rhinitis, rhinoconjunctivitis and flexural eczema in their primary schoolchildren [17]. The prevalence of rhinitis and rhinoconjunctivitis also increased in older Thai children, but asthma prevalence was either unchanged [for Bangkok] or lower [for Chiang Mai]. On the other hand, a Taiwanese study reported an annual increase of 6.5% in the incidence of hospitalization for childhood asthma based on the National Health Insurance data from 1996 to 2002 [18].

Foods, in particular cow's milk, are the first allergens that infants are exposed to right after birth. Food is also the most common eliciting factor of childhood anaphylaxis. When these children with food allergy grow older, their allergies "march" from gut and

skin to the respiratory tract that comes in contact with inhalant allergens such as house dust mites, pet and pollens. As a consequence, these preschoolers develop signs and symptoms of asthma and allergic rhinitis [19]. Thus, epidemiological data on food allergy will help projecting the burden of allergic diseases in our younger generation.

A territory-wide questionnaire study investigated the prevalence of adverse food reactions [AFR], as a surrogate of food allergy, among local children attending 21 randomly selected nurseries and kindergartens in 2004/2005 [20]. The prevalence rates of self-reported AFR and self-reported and physician-diagnosed AFR were 8.1% and 4.6%, respectively. The occurrence of AFRs in these preschoolers adversely affected quality of life of their parents [21]. Shellfish was the most important food for AFR, which was followed by egg, peanut, cow's milk, beef, tree nuts and fish. Another local study supported our above findings [22]. These figures suggested similar epidemiology and spectrum of food allergy between our Chinese and White children [23-25]. Because questionnaire data was open to biased reporting, we also collected data for probable food allergy that was defined as the presence of suggestive clinical features and either positive skin prick test or *in vitro* allergen-specific IgE assays [26]. The prevalence of probable food allergy was 2.8% in our primary schoolchildren [27]. Shek et al. also reported shellfish allergy to be common in Singaporean children, whereas the prevalence rates for peanut and nut allergies were low [28].

In a recent study, our group adopted the same sampling strategy and methodology as our earlier one [20] to investigate longitudinal changes in food allergy prevalence among our Chinese preschool children [29]. The prevalence of parent-reported AFR was 9.7%, but there was no change for parent-reported, doctor-diagnosed AFR. When adjusted for maternal education as covariate, the prevalence for parent-reported AFR was in fact static whereas that of parent-reported, doctor-diagnosed AFR significantly decreased during this 9-year period.

Maternal diet during pregnancy and lactation

Maternal Diet during Pregnancy

A healthy diet during pregnancy is both important for maternal and fetal health. For food allergy prevention, it is universally recommended for all mothers to include a healthy diet without restriction during pregnancy [30-32]. Prophylactic dietary restriction on potent food allergens should not be encouraged during pregnancy [31,33-35], as it is unlikely to reduce risk of atopic diseases in infants [7,30,35-36]. During the first trimester, higher maternal intakes of peanut, milk, and wheat were associated with a significant reduction in the risk for developing a peanut allergic reaction, asthma and allergic rhinitis, and atopic dermatitis in mid-childhood, respectively [37]. In addition, a restrictive diet may have adverse effects on maternal or fetal nutrition [34-35,38].

Studies on diet in pregnancy reveal that consumption of fruits and vegetables, fish, long-chain omega-3 fatty acids, a good ratio of omega-3 to omega-6 fatty acids, and milk fat is associated with a lower prevalence of allergy [31,39]. The consumption of fruits and vegetables is beneficial for their content of antioxidant [33] and natural prebiotics [31], which has been suggested to have preventive effects by promoting a more diverse microbiota and consequently a positive effect on fetal immune development [40].

The consumption of fish during pregnancy has a protective effect in the development of atopic diseases in children [31,41-44]. Children of mothers consuming fish 1 to 4 times a month was associated with a lower risk of wheeze before age two [45], and a weekly maternal fish intake of more than 205grams was associated with lower risk of infantile eczema [43]. Furthermore, a Danish cohort found that high fish intake in pregnancy is associated with lower risk for early asthmas in mid childhood [46]. In randomized-controlled trials, fish oil intake during late pregnancy was also associated with lower risk of asthma [47], and prenatal supplementation of long chain omega-3 fatty acid were associated with a lower risk of egg sensitization and atopic eczema in their children up to 1 year of age; however, there is no difference in the risk of IgE-mediated food allergies [42]. The current German guidelines recommends that fish consumption can be encouraged in pregnancy [31].

While fish intake during pregnancy has positive effects in preventing atopic diseases, shellfish consumption more than once a month may increase the risk of food allergies [45]. Moreover, in a German cohort study, increased prenatal intake of margarine and vegetable oil is associated with increased risk of eczema in children, while increased prenatal intake of celery and citrus fruits are associated with increased risk for sensitization to food allergens in children [44]. In addition, increased prenatal intake of deep-frying vegetable fat, raw sweet pepper, and citrus fruits is associated with increased risks for sensitization to inhalant allergens. Another cohort study about maternal diet also found that intakes of citrus fruits and total fruits are positively associated with sensitization to inhalant allergens [48]. However, the significance of these needs further research to confirm.

Maternal intake of vitamin D is associated with lower risk of food allergen sensitization in offspring [48]. Probiotics may prevent the development of eczema [33]. In the recent guidelines by the World Allergy Organization, the risk of eczema was reduced by 28% in children whose mothers received a probiotic during pregnancy [49]. Most probiotic studies involve the use of probiotics for at least 3 months during pregnancy. The WAO recommends the use of probiotics in the prevention of eczema in infants of high-risk families, but not other allergies [49]. Most of other major allergy authorities do not have any recommendation on probiotics, and the EAACI does not recommend the use of probiotics based on lack of evidence in prevention of food allergy [30].

Maternal Diet during Lactation

All mothers who are lactating should consume a healthy diet for healthy growth of their children [30-31,49]. Studies looking at the effect of food avoidance during lactation have been criticized with methodological shortcomings and small sample sizes [35], and more research is required in this area. Currently, there is no evidence on maternal dietary avoidance of potent food allergens during breastfeeding in the prevention of food allergy in their children [30,33-36,50]. Recently, the WAO reported that mothers with probiotic supplementation during lactation period are associated with a 39% risk reduction of eczema in their infants [49], and it is recommended for families with high risk for food allergies.

Infant Feeding

Breast Feeding

For all infants, breastfeeding is recommended for at least first 4 to 6 months of life [30-34,51]. Breastfeeding has many physiological and psychological benefits for both mothers and infants, and the World Health Organization recommends that infants

should be exclusively breastfed for the first 6 months of life in order to achieve optimal growth, development, and health [51]. Because it would be unethical to randomize infants to breastfeeding or formula feeding, there have not been any long-term studies comparing breastfeeding to formula feeding [34,52]. Evidence suggests that exclusive breastfeeding for at least 3 months reduces the risk of atopic dermatitis in infancy while data is weaker for other allergic diseases [52] . When compared with conventional cow's milk formula, breastfeeding has a significant protective effect against atopic dermatitis [51] and wheezing in the first 2 years of life [53]. Furthermore, breast milk might play a role in the development of oral tolerance [54]. However, there is insufficient evidence to conclude its preventive effect on the development of food allergies [33,34,50,52].

Formula Feeding

For infants at high risk of atopy and who are not exclusively breastfed for 4 to 6 months, hydrolyzed formula feeding may be able to delay or prevent the onset of atopic disease compared with formula with intact cow's milk protein [30-34,51]. The GINI study's 10-year data shows that in high risk infants, the incidence of atopic eczema was significantly reduced in those consuming extensive hydrolyzed casein formula and in those consuming partially hydrolyzed whey formula [55], compared to standard cow's milk formula. There was no significant result related to extensively hydrolyzed whey formula [55]. Studies have shown slight benefit of extensively hydrolyzed casein

formula compared with partially hydrolyzed formula [56,57]. While other studies show that extensively hydrolyzed whey is effective in preventing food allergies in babies, a large German cohort study shows that partially hydrolyzed whey formula is more effective than extensively hydrolyzed whey formula [56]. This may indicates that the degree of hydrolysis alone does not explain the preventive power of a formula [30,51]. There is no evidence on the use of soy formula [30,31,33] or goat formula [33] in the prevention of food allergies, while amino acid formula have not been studied [34].

On the contrary, a recent prospective study has found that children who have early introduction of cow's milk formula (<14 days) have less incidence of IgE-mediated cow's milk allergy compared to those with later introduction (104-195 days), suggesting that the early feeding of cow's milk protein may prevent IgE-mediated cow's milk allergy [58]. More research is needed to confirm this observation [34].

Introduction of Complementary Foods

According to European data, about one-fourth of children start solid introduction before 4 months of age, and most of the children would have eaten solids by 6 months of age [36,59]. In addition, formula-fed children tend to start complementary feeding earlier.

Introduction of complementary foods is recommended for infants over 4 months, and there is no benefit of delaying introduction beyond 4 to 6 months for the prevention of allergic diseases [30-33,50,51,60-62]. One study shows that weaning above 16 weeks of age was associated with increased risk in food hypersensitivity at age one [36]. However, a recent case-control cohort study found that children diagnosed with food allergies by age 2 years are more likely to have introduced solid foods at less than 16 weeks [63]. Other earlier studies have also found that introduction of solids before 4 months was associated with increased risk of allergic diseases [36]. An infant diet consisting of high levels of fruits, vegetables, and home-prepared foods is associated with less food allergy by the age of 2 years [61,64]. In addition, there may be some benefits of weaning while still breastfeeding to prevent the onset of allergies [60,63]. When introducing complementary foods, consideration of developmental readiness, parental needs, nutritional needs and behavioral risks of the infant should be made, and some suggests there should not be a strict timetable for introducing new foods [60].

Introduction of potential food allergens

Earlier guidelines have recommended late introduction of allergenic foods [59], and it has been common practice to delay introduction of food allergens in high-risk infants. However, later evidence in animal studies has been suggesting that there is a critical window of opportunity for the introduction of food protein, which is likely to be between

4 to 6 months of life in humans [65]. There is emerging evidence suggesting that delaying solid food introduction beyond 6 months, especially with potent food allergens, may increase the risk of food allergy or eczema [33,54,60]. Data from a Finnish cohort study indicate that late introduction of potatoes, oats, rye, wheat, meat, fish and eggs was significantly directly associated with sensitization to food allergens [66], while late introduction of potatoes, rye, meat, and fish was associated with inhalant allergen sensitization. Recently, the LEAP study has demonstrated that consumption of peanut within the first year of life in high risk infants can lower the chance of peanut allergy compared to avoidance until age 5 years old [7]. Another randomized controlled trial found that infants exposed to whole egg powder daily starting at 4 to 8 months have higher egg-specific IgG_4 levels compared to control group [67]. Furthermore, a Swedish prospective, longitudinal cohort study found that introduction of fish before 9 months of age is associated with lower risk for eczema [62] and this has been recommended by one of the national guidelines [31].

A "dual-allergen-exposure hypothesis" has proposed that food sensitization can occur via cutaneous exposure and the early oral introduction of the food can induce tolerance [54]. More importantly, the timing of oral introduction is crucial to whether a child will develop allergy. While this hypothesis is being explored, prophylactic avoidance of potent food allergens is not recommended as a measure to prevent food allergy [30,31,33,34,59,61]. However, there is not enough evidence to recommend encouragement of early introduction of all potential food allergens [68]. The current

recommendation is neither to withhold nor encourage early introduction of any food allergens [30-33,60]. Breastfeeding during the period of solid food introduction is likely to attenuate any allergic response.

Prebiotics and Probiotics in Infants

There have been numerous studies investigating the effect of probiotic and prebiotics supplementation during infancy toward allergy prevention. When given to high-risk infants, probiotics have not been shown to have protective effects for food allergy prevention from randomized control trials [69]. A recent meta-analysis of 14 studies has shown a preventive effect of the use of probiotics during pregnancy and early infancy on the risk of atopic dermatitis by 21% [69]. In addition, a recent Cochrane review of 4 studies reports that prebiotics is associated a 32% reduction in the risk of atopic dermatitis [70]. For the effects of probiotics on risk of atopic dermatitis, the World Allergy Organization has recently published its guidelines on the use of probiotics for allergic disease prevention supporting the use of it in high risk infants [49]. However, this view is not supported by some of the literature [50], and the recent guidelines by EAACI do not recommend the use of probiotic based on lack of evidence in prevention of food allergy [30].

Environmental Influence on Allergy

Overview

It is now recognized that environmental factors exert very important effects on the development of allergy, especially in genetically vulnerable individuals, both pre- and postnatally. Environmental potentiating factors range from air pollution, tobacco smoke, early viral infections to aeroallergens. On the other hand, living in a farming environment seems to offer protection. Recent evidence suggests that environmental factors are more related to the development of respiratory allergies. Recognizing and assessing the importance of these factors will allow individuals to consider avoidance or manipulative measures to lessen the chance of developing allergic diseases.

Air pollution

It has long been recognized that atmospheric air pollution is associated with exacerbation of asthma and allergic rhinitis, and is blamed for surges of asthmatic admissions [71,72]. In the past decade, a lot of epidemiological evidence has linked exposure to traffic air pollution [TAP], especially diesel exhaust particulates [DEP], oxides of nitrogen [NOx], and soot [carbon dust] to the development of asthma, allergic sensitization and compromised lung function [73-79]. In a Swedish cohort, exposures to

traffic-related NOx and coarse particulate matter [particles with aerodynamic diameter of 10μm or less, PM10] during the first year of life were associated with increased sensitization to inhalant allergens in addition to increased risk of wheeze and lower lung function at an age of 4 years [77]. As part of a longitudinal birth cohort study, infants living within 50 metres of a main road had increased odds of runny nose and sneezing during the first year of life [80] and increased odds of sensitization to inhalant allergens and asthma at an age of 4–6 years [74]. Other cross-sectional analyses showed measures such as distance to point pollution source and distance to major road or highway were associated with asthma incidence, wheeze, and exacerbation of asthma [81,82]. Another report investigated the relationship between traffic-associated pollution and eczema in children aged 6 years. They found that eczema prevalence was significantly higher in children who lived in traffic-related, highly polluted areas [83].

Mechanisms implicated in the association between air pollution and pediatric asthma include the up-regulation of allergic immune responses, activation of oxidative stress pathways, and epigenetic regulation [84].

In conclusion, there is strong epidemiological evidence linking traffic air pollution and allergic sensitization and the development of allergic diseases like eczema, allergic rhinitis and asthma. Measures to lower exposure to TAP should therefore be logically recommended to prevent allergic diseases.

Tobacco smoke

The effect of both active [AS] and passive smoking [PS] on the development of allergic diseases in adults and children have been recently summarized in a meta-analysis [85] and a review article [86]. When all studies including cohort, case-control and cross-sectional studies were included, allergic rhinitis was not associated with AS (pooled RR, 1.02 [95% CI 0.92–1.15]), but was associated with PS (pooled RR 1.10 [95% CI 1.06–1.15]). Allergic dermatitis was associated with both AS (pooled RR, 1.21 [95% CI 1.14–1.29]) and PS (pooled RR, 1.07 [95% CI 1.03–1.12]). In children and adolescents in particular, allergic rhinitis was associated with both AS (pooled RR, 1.40 [95% CI 1.24–1.59] and PS [pooled RR, 1.09 [95% CI 1.04–1.14]). So was allergic dermatitis associated with both AS (pooled RR, 1.36 [95% CI 1.17–1.46]) and PS (pooled RR, 1.06 [95% CI 1.01–1.11]). Among cohort studies, PS was significantly associated with an increased risk of food allergy [RR=1.43; 95% CI 1.11–0.83] in children and adolescents. From the studies, it can be seen that the effect of tobacco smoke is more severe on children and adolescents compared with those on adults. Although the increase in allergic disease associated with smoking seems modest, in countries with high smoking prevalence, the authors estimated that 14% of allergic rhinitis and 13% of allergic dermatitis are attributable to active smoking [87].

The European Community Respiratory Health Survey, a multicenter cohort study of asthma, allergy, and lung function since the 90's, has reported the effects of PS from

foetus to adulthood [87-89]. Maternal smoking during pregnancy, maternal smoking, or both parents smoking were more likely to report wheezing in the past 12 months and three or more asthma symptoms, even after accounting for their own smoking behavior, exposure to PS and occupational exposures [86]. Total IgE levels were higher in smokers than non-smokers. The smokers were more likely to be sensitive to house dust mite but not cat or grass. PS was significantly associated with bronchial responsiveness to Methacholine and with current asthma (OR, 1.9 [95 % CI, 1.2–2.9]).

In conclusion, tobacco smoke exposure, whether active or passive, are significant environmental factors in the development of allergic diseases and should therefore be avoided.

Indoor Environment

Home dampness was highlighted as a most important modifiable factor in the home environment to be associated with wheeze ever and recurrent wheeze in one study [90,91]. Similarly, a meta-analysis from 8 European birth cohorts showed that exposure to visible mold and/or dampness during the first 2 years of life was associated with an increased risk of developing asthma, including early asthma symptoms and asthma later in childhood [92]. In another study, high visible mold in the home environment was also associated with recurrent wheeze at age 3 years and a positive Asthma Predictive Index

[93]. Other risk factors at home that have been reported to be associated with recurrent wheezing include use of foam pillow and exposure to gas cooking fuel [94].

On the other hand, exposure to a farming environment has been well studied. A recent review and meta-analysis reported an overall 25% reduction of doctor diagnosed asthma and recurrent wheeze in children exposed to a farming environment [95]. An older review article examined the effect of the farming environment on allergic rhinitis and eczema, and concluded that farm living had a substantial protective influence on the development of allergic stigmata [96]. The mechanism of effect of farm exposure on allergy development has been thought to be related to raw farm milk consumption [97] and/or exposure to a wider range of micro-organisms in the farm, and its resultant gut microbiome [98].

Allergens exposure, especially to house dust mite allergen, has been implicated as a possible cause of allergic asthma. Many studies have attempted to prevent allergies and asthma by controlling HDM and other allergens in the home environment. A recent meta-analysis [99] reported a significant reduction in physician diagnosed asthma as a result of interventions to reduce exposure to HDM [RR = 0.74; 95% CI, 0.58–0.95]. However, there was no significant effect on parent-reported wheeze [RR = 0.95; 95% CI, 0.78–1.15]. This may suggest that reduced exposure to house dust prevents the more severe form of asthma but not the more common and milder forms, which may not be allergic in origin.

The situation with other allergens is not as clear. As a study on the effects of pet ownership in the first year of life on respiratory symptoms in children aged 7 years shows [100], there was a significant relation between the exposure to cat allergens and current wheezing in childhood [OR = 1.88], which cannot be observed in children with contact to dogs instead. The Canadian high-risk birth cohort [101] compared the role of different indoor allergens in pediatric allergic patients. In this study, early life or elevated HDM exposure was associated with the risk of sensitization but not asthma, while the opposite was true for dog exposure. On the other hand, a pooled analysis on over 22,000 children participating in 11 European birth cohorts concluded that there was neither an increase nor reduction in the risk of asthma or allergic rhinitis symptoms in children aged 6–10 years in relation to pet ownership in early life [102].

In conclusion, dampness, visible mold, and HDM are important indoor factors in the development of allergic disease. The control of these factors is likely to lead to a lesser chance of development of allergic disease including asthma. Although a farming environment is known to be associated with a lower incidence of allergy. Recommendation is still difficult and awaits further analysis of the mechanism of action.

Viral respiratory infections

Early viral respiratory infections have been implicated to be associated with the development of asthma and other respiratory allergies later in life [103, 104]. Human rhinovirus [HRV] and Respiratory Syncytial Virus [RSV] have been found to be associated with a markedly higher risk of persistent wheezing at 6 years of age [105,106]. Another study on over 2000 children confirmed an increased risk of new-onset wheeze at age 2 years for children suffering from childhood infections like common cold, fever, and diarrhea during the first 3 months of life [107]. The findings were supported by another study [108].

In conclusion, present evidence suggests that early viral infections, especially by HRV or RSV, are associated with an increased chance of allergy development. Preventive strategies, apart from general infection control measures, consist of giving RSV immunoglobulin to vulnerable infants.

Lifestyle

Overweight and obesity

Healthy lifestyle with a good balance of calorie intake and expenditure should be encouraged. Recent meta-analysis has revealed that overweight poses an increased risk of asthma. This risk is further elevated in obese subjects with a clear dose-response relationship between the body mass index [BMI] and the risk of asthma [109]. European

birth cohorts recruiting more than 12,000 subjects have demonstrated a rapid rise of BMI in the first 2 years of life increased the risk of asthma up to 6 years old [110]. There is also a significant association between overweight/obesity and eczema [111]. Thus, in addition to its other well recognized health benefits, excessive body weight should be avoided to help preventing the development of allergic diseases.

Early natural immune stimulation

Early natural immune stimulation has protective effects against allergic diseases. A recent meta-analysis revealed a statistically significant risk reduction of around 25% for development of asthmatic symptoms with exposure to natural farming environments during the childhood period [112]. But there is also substantial heterogeneity of the effects across studies. According to the cohort results of the Protection Against Allergy: Study in Rural Environments [PASTURE], it was noted that the risk of childhood eczema in the first 2 years of life decreased as the maternal exposure to animal species during pregnancy rises. The risk of eczema was decreased by >50% among children whose mothers having contacted ≥3 farm animal species during pregnancy [113].

Psychosocial factor

More and more studies are now showing that adverse psychosocial factors during pregnancy and childhood can contribute to the onset of atopic diseases. A growing number of studies indicate that experiencing stressful life events (e.g. parental separation, death of a parent, parental unemployment), either during pregnancy or in early childhood, increases the risk of subsequent atopic diseases [114-117]. Early therapeutic counselling could represent a preventive approach in these children.

Pharmaceuticals & Immunotherapy

Antibiotics and paracetamol

Although some studies suggested an association between pharmaceutical drug use (in particular antibiotics and paracetamol) and atopic diseases, these results should be interpreted with caution due to potential reverse causality and confounding factors. Subgroup analysis of studies minimising reverse causality indicates that these associations were no longer significant [118]. At present, no causal relationship was found between the use of these pharmaceutical drugs and the development of atopic diseases.

Bacterial lysates

A randomised placebo-controlled trial on the prophylactic use of bacterial lysates showed no effect on the primary endpoint, but a significant reduction in eczema was noted in the subgroup of children having one atopic parent [119]. The use of bacterial lysate might have a role in the prevention of eczema in high risk children with a family history of atopy. Further studies are ongoing to delineate its safety and efficacy.

Vaccinations

There is no evidence to show that vaccination practices have any adverse effect on the incidence of allergic diseases in population-based cohort studies [120,121]. Children are recommended to receive vaccinations according to the current recommended schedule, including those high risk children.

Vitamin D

Clinical studies have produced conflicting results with regard to the relevance of vitamin D in the development of allergic diseases [122-123]. There is currently insufficient data to support the formulation of a recommendation.

Immunotherapy

Immunotherapy, both subcutaneous or sublingual, have been shown to be effective in patients suffering from allergic rhinitis, allergic conjunctivitis and asthma, especially in those patients with definitive sensitization to specific allergens [125-129]. A number of small studies, including one randomized trial of 51 patients, also showed that it is an effective treatment modality in the management of eczema for those sensitized patients [130-131]. Larger scales studies are underway to delineate further its efficacy in treating eczema.

It is also an important tool in the secondary prevention of allergic diseases. There is evidence showing that immunotherapy of allergic rhinitis can prevent the subsequent progression to asthma [132-136]. It can also reduce new sensitisations in patients mono-sensitised to aeroallergens and has an impact on the natural history of respiratory allergies [136-139].

Conclusion

The strengthening of immune tolerance is the current focus in allergy prevention. Besides allergen avoidance, further studies are now underway to investigate how immune tolerance can be boosted to different allergens, while minimizing sensitization and further allergic responses. In general, it is noticeable that the greater the exposure to environmental and commensal microbes in terms of diversity and quantity during infancy

and early childhood, the greater the development of immune tolerance and lesser the atopic tendency, even in those who are genetically susceptible [140].

From the above discussions in this guideline, we can summarize and list the recommended allergen prevention measures into Appendix I. For those who are at higher risk of allergy development, i.e. those with a family history of allergy or the presence of several risk factors, (e.g. breast fed for <6 months; maternal active or passive smoking during pregnancy; delivered by Caesarian section), it is recommended that they observe the allergy prevention measures and consult a medical doctor early should they develop clinical features of allergic diseases. In order to help those who are at increased risk of allergy to identify their own risk of allergy development, there are a number of allergy risk screening tools published already [141-144]. However it should be noted that in most instances these 'allergy screeners' have not been rigorously validated. We strongly recommend that validation of these questionnaires should be urgently undertaken.

Besides recommendations on a personal level, the development of a community based action plan would be greatly beneficial and cost effective. The implementation of National Asthma and Allergy Plans had already shown that the burden and cost of allergic diseases could be reduced by a concrete and pragmatic public health action plan [145]. One good example is the Finnish Asthma Programme, which is a successful model showing that community based public health measures can improve nationwide asthmatic outcomes. Owing to the success and the favourable outcomes, the second phase of the expanded program, the Finnish Allergy Programme, is now being

implemented to combat the development of allergies by promoting lifestyle measures to strengthen immune tolerance in early life and by carrying out early interventions for allergic diseases. A successful community based programme requires the contributions from various stakeholders for effective implementation. Educational campaigns and networking between specialists and primary care doctors, pharmacists, nurses, teachers, parents, allergic patients and general public should be promoted.

The treatment modalities for allergy are still relatively limited at present, so prevention is the key to control this pandemic. Allergic diseases in Hong Kong and worldwide have increased dramatically in the past few decades. It is still on the rise in Hong Kong from the latest epidemiological data. It is now pressing and timely to implement allergy prevention and promote a healthy lifestyle for the Hong Kong population and beyond [146].

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Appendix I Allergy Prevention Measures

1. No unnecessary diet restriction during pregnancy and lactation
2. Breastfeeding in the first 6 months of life
3. Consider hydrolyzed formula milk if exclusive breastfeeding is not feasible in high risk infants
4. Introduce complementary food from 4-6 months of age when developmentally ready
5. Control air pollution
6. Avoid smoking, both active or passive smoking
7. Control indoor air quality
8. Weight control and avoid obesity
9. Avoid excessive psychological stress
10. Immunization as recommended
11. Judicious use of antibiotics
12. Early treatment and control of atopic diseases