consumption group (p<0.001). Among the 98 participants in the ITT population who initially had positive test results, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group (p=0.004).

- The EAT study randomly assigned 1,303 exclusively breastfed infants at 3 months of age to early introduction of 6 allergenic foods or to exclusive breastfeeding to approximately 6 months of age.[29] In the per-protocol analysis, the prevalence of any food allergy (2.4% vs 7.3%; p=0.01), peanut allergy (0% vs 2.5%; p=0.003) and egg allergy (1.4% vs 5.5%; p=0.009) was significantly lower in the early-introduction group than in the standard-introduction group.

Guideline recommendations

As a result of the growing body of evidence, international guidelines are now changing to recommend solid food introduction – including allergenic foods – by 4–6 months. Locally, the 2016 Guidelines for Allergy Prevention in Hong Kong recommended practical measures, starting from pregnancy, for allergy prevention (Figure 4).[23]

- No unnecessary diet restriction during pregnancy and lactation
- Breastfeeding in the first 6 months of life
- Consider hydrolyzed formula milk in high-risk infants if exclusive breastfeeding is not feasible*
- Introduce complementary food from 4 to 6 months of age when developmentally ready
- Control air pollution
- Avoid both active and passive smoking
- Control indoor air quality
- Control weight and avoid obesity
- Avoid excessive psychological stress
- Receive immunizations as recommended
- Judicious use of antibiotics
- Early treatment and control of atopic diseases

* The GINI study was a landmark trial that investigated the effects of partially hydrolyzed whey formula (pHF-W), extensively hydrolyzed whey formula (eHF-W) and extensively hydrolyzed casein formula (eHF-C) versus cow's milk formula (CMF) – given in the first 4 months of life – on the prevention of allergy in high-risk infants.[30] At 12 months, the incidence of allergic manifestation was significantly reduced with eHF-C compared with CMF, while AD incidence was significantly reduced with both eHF-C and pHF-W. At 15 years, there was a significant positive impact on respiratory allergies with hydrolyzed infant formulas compared with CMF.[31] The cumulative incidence of eczema was also significantly lower with eHF-C and pHF-W (versus CMF).[31]

Figure 4. Allergy prevention measures[23]

Conclusion

Maternal nutrition, infant nutrition (particularly in the first 1,000 days of early life) and immunity are inextricably linked. The early manipulation of the microbiome is a good opportunity for protecting human health. Major advances in allergy research have revealed a window of opportunity in early life for prevention and treatment, and caused a paradigm shift from allergen avoidance to tolerance induction.

Clinicians can advise women on the importance of proper nutrition during pregnancy, and of early-life nutrition, for the health outcomes of their child. When a balanced diet of fresh, whole foods cannot be maintained, nutritional supplementation, eg, of probiotics, vitamin D and n-3 PUFAs, in the right doses may be considered to help promote a healthy microbiome and immune system for both mothers and infants; based on current data, these nutrients are not harmful, and may be beneficial for fetal development and the immune system.[32,33]

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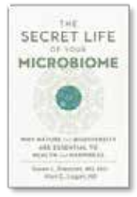

THE SECRET LIFE OF YOUR MICROBIOME
Why Nature and Biodiversity are Essential to Health and Happiness
Dr Susan L Prescott, MD, PhD & Dr Alan C Logan, ND

Written with pace, clarity, and humor by world-renowned scientists in immunology, nutrition, and environmental health, this book makes the irrefutable case that our health and happiness depends fundamentally on the health of our personal biodiversity and the biodiversity around us, and shows how we can nurture this nature.

Sponsored as a service to the medical profession by Nestlé NutritionInstitute

Maternal and infant nutrition: Gut microbes and immune programming for health promotion in an era of dysbiosis

A recent dinner symposium organized by the Hong Kong Institute of Allergy, titled 'Early Nutrition as a Major Determinant of Gut Microbes, Immune Health and Allergy Prevention', featured Professor Susan Prescott (Australia) and Dr Alson Chan (Hong Kong). Chaired by Dr Marco Ho, President-Elect of the Hong Kong Institute of Allergy, the symposium centered on the role of the gut microbiome in immune health, and how maternal and early-life nutrition can positively influence long-term health outcomes. Professor Susan Prescott was also the keynote speaker at a lunch symposium of the 25th Asian & Oceanic Congress of Obstetrics and Gynaecology. This report includes highlights of these presentations, and an interview with Professor Prescott.

Professor Susan Prescott
Professor, School of Paediatrics and Child Health
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The critical role of early-life nutrition in immune programming and allergy prevention

The immune system is a critical determinant of health, longevity, resilience and susceptibility to disease. The development of a healthy immune system involves a complex interplay between factors such as maternal and infant nutrition, the microbiome, and the external environment, and these factors also play a role in other body systems throughout life.

Nutrition in early life heavily influences the establishment of a healthy, balanced gut microbiome. Also, lifestyle factors such as inactivity, obesity and stress take root in influencing fetal immune function from birth.[1-3] Importantly, there appears to be a critical window – in the first 1,000 days of life – wherein nutrition is particularly crucial for future development, with a potential lifelong impact on metabolism, immune function and neurodevelopment.[4] Thus, if the goal is to promote development of a healthy microbiome leading to a healthy immune system, timing is key for any nutritional strategy.

In terms of clinical implications, early nutritional habits and microbial exposure may affect an individual's long-term risk of inflammation.[1-3]

Several studies have also shown that impaired microbial diversity (dysbiosis) during the critical window of the first 1,000 days of life increases the risk of allergic diseases later on.[5,6] In general, the dramatic rise in allergic diseases in children, and noncommunicable diseases (NCDs) in adults, partly reflects the vulnerability of the immune system to changes in the environment and lifestyle. Although many NCDs begin in adulthood, processes leading to their development are likely to be programmed in early life.

Improving the gut microbiome through nutrition

The best way to optimize gut health is through a healthy and balanced diet. Food influences health and immune function through multiple pathways (Figure 1). Together with the erosion of environmental biodiversity, the stereotypical unhealthy Western diet is a major factor in dysbiotic gut microbiomes and the rising risk of NCDs.

Modifying food intake to include more fiber, more n-3 polyunsaturated fatty acids (PUFAs; also called omega-3 fatty acids), less fat, less salt, more fresh foods, micronutrients and vitamins, has favorable effects on immune function, mood, appetite, and fat and glucose metabolism. Indeed, changing the diet may be one of the quickest ways to improve gut microbiota.

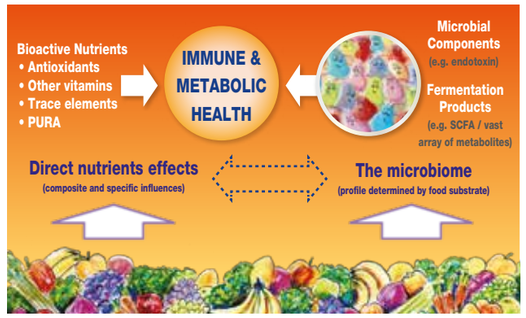

Figure 1. Broad mechanisms by which food influences health and immune function

Nutritional supplementation

Probiotics and prebiotic supplementation is regarded as a safe and relatively simple strategy for restoring gut health in cases of dysbiosis and may help in disease prevention. For example, the use of probiotics has been recommended by several expert bodies for allergy prevention, although more data are required to determine the exact role of probiotic and prebiotic supplementation in health and medicine.[7,8]

Prebiotics. There is some evidence on the beneficial effects of prebiotics on immune parameters,[4,9] and for protection against infection and allergies,[4,10] but robust

data are mostly insufficient or inconsistent. The World Allergy Organization (WAO) guideline panel suggested using prebiotic supplementation in infants who were not exclusively breastfed, but not in exclusively breastfed infants. These recommendations were conditional and based on a very low certainty of the evidence; **no specific recommendations were made for prebiotic supplementation in pregnant or breastfeeding women.**[7]

Probiotics. According to the WAO guideline panel, considering all critical outcomes, there was a net benefit from probiotic use in eczema prevention.[8] Although the timing, duration and choice of probiotic were not specified, the panel suggested[8]:

- Using probiotics in pregnant women at high risk of having an allergic child;
- Using probiotics in women who were breastfeeding infants at high risk of developing allergy; and
- Using probiotics in infants at high risk of developing allergy.

Other studies have also shown that probiotics provide some protection against eczema and childhood infection.[11,12] For example, there is strong evidence that probiotic supplementation prevents severe necrotizing enterocolitis and all-cause mortality in preterm infants.[13]

Clinicians can guide mothers on the use of probiotic products that have been clinically studied, such as Lactobacillus rhamnosus GG, Lactobacillus acidophilus, Bifidobacterium lactis and Bifidobacterium bifidum.

Vitamin D. Data from the HealthNuts study showed that, at 1 year, children with vitamin D insufficiency were around 11 times more likely to have a peanut allergy and 4 times more likely to have an egg allergy than those with adequate vitamin D levels.[14] Vitamin D insufficiency was also significantly more common in infants with 2 or more food allergies than in infants with 1 food allergy (p=0.045).[14] In terms of possible mechanism, adequate vitamin D status in pregnancy or early infancy might reduce allergic disease development in high-risk infants via inhibition of cytokine profiles that may lead to allergy.[15]

A daily dose of 600 international units (IU) (15 µg) is safe for all age groups, and is recommended for all pregnant women (Figure 2).[16,17] The Centre for Food Safety in Hong Kong recommends a daily allowance of 200 IU (5 µg), according to the Chinese Nutrient Reference Value derived for the Chinese population.[18] Major sources of vitamin D include salmon, tuna and mackerel, and fish liver oils, as well as vitamin D-fortified food. Small amounts of vitamin D are found in beef liver, cheese and egg yolks.

Age	Male	Female	Pregnancy	Lactation
0-12 months*	400 IU (10 mcg)	400 IU (10 mcg)		
1-13 years	600 IU (15 mcg)	600 IU (15 mcg)		
14-18 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
19-50 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
51-70 years	600 IU (15 mcg)	600 IU (15 mcg)		
>70 years	800 IU (20 mcg)	800 IU (20 mcg)		

Figure 2. Recommended dietary allowances for vitamin D[17]

n-3 PUFAs. n-3 PUFAs and fish oils have extensive anti-inflammatory effects, and the effects in pregnancy and NCDs have been well studied. A recent Cochrane meta-analysis of randomized controlled trials of n-3 LCPUFA supplementation in pregnant and/or breastfeeding women, on the allergy outcomes of their children, found that supplementation resulted in a clear reduction in medically diagnosed IgE-mediated allergies in children aged 12–36 months.[19] Maternal supplementation of n-3 PUFAs also reduced the occurrence of food allergies in children aged 0–12 months, and distinctly reduced sensitization to egg and to any allergen in infants aged 12–36 months.[19]

The majority of scientific research into n-3 PUFAs has focused on alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Adequate daily intakes are shown in Figure 3.[20] Natural sources of n-3 PUFAs include plant oils that contain ALA (flaxseed/-linseed, soybean and canola oils), chia seeds and black walnuts. Salmon, mackerel, tuna, herring and sardines also contain high amounts of n-3 PUFAs, and many foods fortified with n-3 PUFAs and dietary supplements are also available.

The European Food Safety Authority recommends a daily intake of 250 mg of EPA plus DHA as being adequate, with an additional 100–200 mg/day of DHA in pregnancy.[21] The Perinatal Lipid Intake Working Group also advises pregnant and lactating women to aim to achieve an average dietary intake of at least 200 mg/day of DHA.[22]

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months*	0.5 g	0.5 g		
7-12 months*	0.5 g	0.5 g		
1-3 years**	0.7 g	0.7 g		
4-8 years**	0.9 g	0.9 g		
9-13 years**	1.2 g	1.0 g		
14-18 years**	1.6 g	1.1 g	1.4 g	1.3 g
19-50 years**	1.6 g	1.1 g	1.4 g	1.3 g
51+ years**	1.6 g	1.1 g		

Figure 3. Adequate intakes for n-3 PUFAs[20]
* As total omega_3s; ** As ALA

An interview with Professor Susan Prescott

Q: In terms of immune programming and allergy prevention, how important is maternal nutrition during pregnancy?

A: Food is the foundation of human structure and function. Poor nutrition during pregnancy has lifelong consequences on many aspects of health – especially immune health. We suspect that the dramatic rise in allergies and immune diseases in early life can be traced back to maternal nutrition during pregnancy. It may not be all about nutrition, but it is one factor. We encourage people to have a balanced diet filled with fresh fruit and natural food. I can't underscore enough how important nutrition is for health.

Q: Which nutrients should women pay particular attention to during pregnancy?

A: We all know the importance of specific nutrients, like iron, folate, PUFAs, probiotics and vitamin D. It is important to keep in mind that while a nutritious diet is always preferred, sometimes, we do need supplements to aid nutrition, but they should never be considered as replacements.

Q: What is the current role of prebiotic and probiotic supplementation in pregnant and lactating women, as well as infants?

A: Probiotic use is supported by some trials and animal studies, although there are currently no specific recommendations. For specific strains and amounts, we can go with what has been used in the studies; if you can find a product that has the strains that have been studied in trials with promising results (eg, Lactobacillus rhamnosus GG), then use those. Clinicians can also guide pregnant women and mothers on the use of probiotics accordingly to guideline suggestions. For prebiotics, there are no specific recommendations, but preclinical trials show promise.

Q: Biodiversity in the gut is critical to allergy prevention and to reducing the risk of developing NCDs. In everyday life, how can we increase our biodiversity?

A: We strongly encourage people to eat a balanced, culturally appropriate diet – traditional diets usually have a natural balance to them. Fermented foods like kimchi, for instance, use microbes that create bioactive metabolites. Avoid highly processed fast food and junk food, excessive sugar (including artificial sweeteners that seem to have adverse effects on the microbiome) and excessive salt.

Microbiome signature: The new era of allergy prevention

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The rising rate of allergic diseases

Over the last 50 years, the prevalence of allergic diseases worldwide has been on an alarming upward trend, and allergic diseases are now of pandemic proportions. This is especially pronounced in children: up to 40–50% of schoolchildren are now sensitized to 1 or more common allergens.[23, 24]

The population-based International Study of Asthma and Allergies in Childhood found that, in Hong Kong, 10% of secondary schoolchildren had asthma, 15% had atopic dermatitis (AD) and about a third of those aged 6–7 years had rhinitis.25

In the 1980s, the hygiene hypothesis was established, and it was proposed that increased microbial exposure in early life may protect children from developing immune hypersensitivity in later life.[26]

Evidence supporting early intervention

A number of studies show that food avoidance in early life may not be the most effective approach for preventing allergies. Rather, the introduction of diverse foods earlier in life may decrease the risk of developing allergic disease:

- The PASTURE/EFRAIM study was the first study to show that infants exposed to an increased diversity of food within the first year of life significantly reduced their risk of asthma, food allergy and sensitization to food allergens up to the age of 6 years.[27]
- The LEAP study randomly assigned infants with severe eczema, egg allergy, or both, to either consume or avoid peanuts until 60 months of age.[28] Among the 530 infants in the intention-to-treat (ITT) population who initially had negative skin-prick test results, the prevlence of peanut allergy at age 60 months was 13.7% in the avoidance group and 1.9% in the