

The Interplay Between Diet and Emerging Allergy: What Can We Learn From Indigenous Australians?

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The pathophysiology of atopic diseases, including asthma and allergy, is the result of complex gene–environment interactions. Since European colonization the Indigenous population of Australia has undergone significant changes with respect to their lifestyle as hunter-gatherers. These changes have had a detrimental effect on Aboriginal health, in part due to immunological modification. This review provides a comparative look at both the traditional Aboriginal/Indigenous diet and modern Western diets, examines some common allergies increasingly reported in contemporary Indigenous populations, and reviews concepts such as the effect of vitamin deficiencies and changes in gut microbiota on immune function.

Keywords asthma, hygiene hypothesis, microbiota, vitamin A, vitamin D

The relationship between diet and health is highly complex and involves the interaction between various systems in the body, potentially causing and preventing disease [1]. Diseases caused by a dysfunctional interaction between food and the body are as numerous as they are broad, ranging from gastrointestinal to respiratory [2–4]. The immune system is at the cornerstone of this interaction [5, 6]. It can be argued that there are four predominant ways that the immune system and diet interact: over-nutrition, such as obesity; undernutrition, for instance, anorexia and scurvy; dysfunctional nutrition, such as food allergy; and via genetic disease, including celiac disease [6–10]. While there is some overlap and interplay among these four interactions (such as the fact that allergy can have a genetic basis), each one can be singularly causal [11]. The immunomodulatory effects of changes in diet are becoming increasingly linked to the escalating prevalence of allergic disorders in Western societies, including allergic rhinoconjunctivitis, asthma, and atopic eczema [12–14]. Allergy in many first world populations is now a major public health burden to both sufferer and governments alike, causing significant morbidity and mortality in the former and massive financial costs in the latter [15, 16].

Since European colonization, the Indigenous population of Australia has undergone significant changes in respect to their lifestyle as hunter-gatherers. This includes changes to diet through westernization of foods, and style of living via urbanization, both of which have appeared to have a detrimental effect on Aboriginal health, in part due to immunological modification. Currently in Australia there is a substantial

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gap between the health of Aboriginal and Torres Strait Islanders and the rest of the population, and improvements in health outcomes for this latter group is a key target of government policies [17]. This review begins with a comparative look at traditional Aboriginal versus modern Western diets, and then examines the connection between diet and the common allergies experienced by Indigenous Australians today, focusing on food allergy and allergic asthma. The role of vitamin D and vitamin A will be examined, followed by an assessment of the effects of gut microbiota (including probiotics) in allergic disease. Finally, the hygiene hypothesis in regard to the effect of parasites on emerging allergy in Australian Aboriginal populations will be examined.

Traditional Aboriginal versus Modern Western Diets and Allergy

The term “traditional diet” here shall refer to the diets of the majority of people pre-20th century and pre-European settlement for the Indigenous population of Australia. As industrialization and population levels have increased globally over the last century, there have been dramatic changes to what people are consuming [18]. According to Cordain et al. there are seven crucial nutritional characteristics of the traditional human diet that have been dramatically altered by westernization: glycemic load, fatty acid composition, macronutrient composition, micronutrient density, acid–base balance, sodium: potassium ratios, and fiber levels [18]. Much of this can be ultimately attributed to an overall shift from a low-fat, high complex carbohydrate, and nutrient-rich diet to one that is the exact opposite [19, 20]. Additionally, while there is a large degree of variance in people’s daily diet around the world due to unique locations (e.g., the availability of kangaroo meat in Australia), generally the overall nutritional values of differing cultures is very similar [18, 20–22].

The traditional diet of the Australian Aboriginal has very homogeneous nutritional values when compared to other traditional diets globally, due to similarities in hunter-gatherer ancestry. The hunter-gatherer lifestyle comprised high-energy expenditure (due to high levels of physical activity) coupled with a nutritionally diverse diet [22, 23]. Many Indigenous populations, including Indigenous Australians, ate red meat as a major component of their diet, yet this did not lead to increased levels of fat due to the lean nature of wild animal carcasses [22, 23]. Seafood was also a major part of many diets (especially in coastal communities), and carried many health benefits due to omega 3 and 6 fatty acids and lean protein content [22–24]. The beneficial nutritional components of these lean meats and fish include long-chain polyunsaturated fatty acids (PUFAs), protein, iron, zinc, vitamin C, and B complex vitamins [22, 25, 26]. In addition many traditional diets included high-level consumption of a large variety of mostly raw plant foods rich in fiber and complex carbohydrates, such as fruits, vegetables, seeds, nuts, and roots [22]. While these foods generally have low energy density, they are rich with a diverse array of nutrients (including several vitamins and proteins) and are slowly processed via the digestive system, including the resident microflora [22, 27].

European colonization resulted in a dramatic change of lifestyle for the Australian Indigenous population [22]. The traditional lifestyle of overall low energy intake (albeit with high nutrient density) coupled with an excessive amount of energy expenditure was completely reversed. Currently, Aboriginal people in urban environments consume a diet with high levels of sugar and fat, deficient in vital nutrients [28]. In addition, Aboriginal people living in rural and remote (RAR) communities are greatly restricted in their access to fresh fruit and vegetables, as well as other varied foods [29,30]. Both groups live a highly sedentary lifestyle when compared to their pre-westernized counterparts, but have retained the custom of eating whatever is provided or available [22, 31]. Traditionally, this custom served the hunter-gatherer well, but

TABLE 1. Dietary shift and health consequences: summary of the health effects of changing from a traditional diet to a westernized diet

Traditional diet	Modern Western diet	General health consequences
Low in fat	High in fat	Obesity, asthma and inflammation
High antioxidants via fresh FAVs	Less fresh FAVs	Inflammation and oxidative stress
Adequate vitamin levels	Vitamin deficiencies	Asthma and less tolerance to food allergens, allergy
Allows for high diversity in gut microbe populations	Lower levels in gut microbe populations	Development of atopy

Note. FAV, fruit and vegetables.

in contemporary Australia it contributes to both obesity and malnutrition, including nutrient waste (for example, excessive water-soluble vitamins will be excreted rather than retained by the body) [22, 31, 32].

Immunity is a multifaceted redundant system that depends on nutrients for optimal functioning [7, 33]. The relationship between diet and allergy includes nutrient dependence, as food components can act as powerful modulators of the immune system at the cellular and molecular level (Table 1) [7, 15, 34, 35]. In addition, clear evidence is emerging that prenatal and infant nutrition has direct effects on both immediate and future health of the individual, including allergic disease development [15, 36]. This is of particular relevance to Australian Aboriginals when considering that the modern Western diet introduced foreign consumables such as cow's milk and hen eggs (known allergens), as well as highly refined and processed foods like fast-food [9, 22, 28, 31]. Eggs collected from wild birds may have formed a component of the traditional Aboriginal diet, but one study suggests eggs from ancient chicken breeds cannot be considered any less allergenic but may be tolerated better due to their smaller egg white fraction [37].

Common Allergies of Modern Australian Indigenous Populations

Asthma

Currently, respiratory disease among Australian Aboriginals along with cardiovascular and cancer-related illnesses account for the predominant morbidity and mortality reported in this ethnic group. Additionally, respiratory disease accounts for the top cause of hospitalization for all specifically defined causes that affect both males and females in the aforementioned group [38]. Respiratory disease along with other health complications contributes to the substantial gap in morbidity and mortality between Indigenous and non-Indigenous Australians, with a massive reduction of 17 years life expectancy observed in the former group [39]. In contrast to other countries that possess both an Indigenous and non-Indigenous population, this gap does not appear to be reducing in Australia.

Asthma is one of the most important respiratory diseases in terms of its associated public health burden, and, significantly, it is also the second most self-reported condition among Australian Aboriginals [38, 39]. In contrast, levels of asthma in non-Indigenous people have fallen Australia-wide. In the 2006 Australian Bureau of Statistics report, 26% of Australian Aboriginals had medically diagnosed asthma at some point in their lives, but some reports put the actual number much higher. Additionally, among Aboriginals as a whole, higher rates of asthma are found among those living in urban environments (17.7%) as opposed to those in RAR regions (12.2%) [39]. This is consistent with data from a Western Australian study of Aboriginal children, where the RAR group had asthma levels 4 times lower than their nonisolated counterparts [41]. However, one study notes children with asthma in the Torres Strait region of northern

Australians have more severe disease than children in urban areas [41, 42]. Importantly, no studies to date have made the distinction between extrinsic, that is allergic, and intrinsic asthma when compiling data regarding Indigenous Australians.

Although scientific data for levels of atopy (defined as a wheal reaction of 3 mm or more to a skin prick test for house dust mite [HDM] extract) in Indigenous Australians are limited, surveys in remote and rural Indigenous communities suggest that atopy levels in these communities are increasing, correlating with the adoption of urban lifestyles. In a cross-sectional study undertaken in 1996, the overall prevalence of atopy in four Aboriginal communities in Queensland, Northern Territory, and South Australia ranged from 21 to 34%, in contrast to a surprisingly low prevalence of current asthma 0.5–3.3% [43]. A similar level of atopy, 36.2%, but with a much higher prevalence of asthma (39.4%), was observed in Indigenous children living in rural New South Wales [44]. In a remote Western Australian Indigenous community atopy was found to be predominantly due to positive skin prick test responses to HDM extract and more common in adults (28.05%) than children (18.3%) [45]. In another Western Australian study, positive skin prick responses were again found to be predominantly due to HDM extract and more common in adults than children in a tropical Aboriginal community (35% versus 24%) compared to being more common in children than adults in a desert Aboriginal community (55.5 versus 46.5%) [46]. High levels of HDM anti-IgE (65%), as measured by serology, were reported for another community in the tropical northwest and the prevalence of asthma was reported at 15% [47].

In a broad sense, asthma can be defined as a chronic inflammatory disease that primarily affects the airways by causing coughing, episodic persistent wheeze, and dyspnea [48, 49]. Many cells, including immune cells (T cells, eosinophils, neutrophils, macrophages, mast cells, and epithelial cells), play an important role in the development of airflow obstruction, bronchial hyperresponsiveness, and other lung dysfunction [48, 49]. Intrinsic asthma is differentiated on the basis of little or no family history of the disease and no specific IgE antibodies (Abs) directed against allergens [50]. However, many studies and articles make clear that it is the extrinsic or atopic variant of the disease that is more prevalent among populations [51–53].

The pathway toward pathology in allergic asthma begins when the individual becomes exposed to an allergen, leading to sensitization of CD4⁺ T_H2 cells and associated release of various cytokines, including interleukins (ILs) 4, 5, 9, and 13 [54, 55]. These ILs respectively allow for IgE production, eosinophils activation, mast cell recruitment and growth, and hyperactive airways [54]. Subsequent exposure to the allergen results in 2 phases of immune reaction: first, an early phase, which occurs 30–60 min postexposure, followed around 4–8 h later by a late-phase reaction [56]. During the early phase, many primary mediators, such as leukotrienes, histamine, and platelet-activating factor (PAF), are released, allowing for the observed bronchoconstriction, vasodilation, and increases in both vascular permeability and mucin secretion [54, 57, 58]. Late-phase reactions are categorized by an intensification of the initial response, with secondary mediators released, including chemotactic factors for eosinophils and neutrophils, IL-4 and 5, PAF, and tumor necrosis factor (TNF), culminating in epithelial cell damage [59–64] (Table 2).

During the early-phase immune reaction an important leukotriene, prostaglandin E₂ (PGE₂), is produced by dendritic cells (DCs) in higher quantities in asthmatics than in the rest of the population [65]. PGE₂ has immunomodulatory properties directly relevant to the pathogenesis of allergic asthma due to its role in Th₂ differentiation [65, 66]. PGE₂ is formed after the bioconversion of linoleic acid to arachidonic acid, and is also be found in foods such as margarine and cheap vegetable oils [66, 67]. Current research is looking into the relationship between dietary intakes of various PUFAs and atopic asthma, due to the aforementioned formation of PGE₂ and its role in causing

TABLE 2. Mediators of extrinsic asthma: a summary of the mediators and their associated pathophysiological effects in both the early and late phases of allergic asthma

Phase of immune reaction	Mediator released	Pathophysiological effects
Early	Leukotrienes	Contributes to local inflammation
	Histamine	Smooth muscle constriction around airways and increased vascular permeability
	PAF	Allows for vasodilation and is a potent chemotactic molecule for eosinophils
Late	CC-chemokine ligand 11	Attracts eosinophils to the site of inflammation where they contribute to pathological remodelling of the airways and Th ₂ cell attraction
	Leukotriene B ₄	Attracts neutrophils and T cells to the site of inflammation, allowing for higher sensitization to allergens
	IL-4	Released by Th ₂ cells (among others) to stimulate IgE production from B cells and contributes to allergic inflammation
	IL-5	Produced from various cell types, this mediator stimulates eosinophils and contributes to inflammation
	PAF	As above
	TNF	A proinflammatory cytokine causing bronchoconstriction and recruitment of additional immune cells

Note. PAF, platelet activating factor; IL, interleukin; TNF, tumour necrosis factor.

increased inflammation and unchecked IL-4 production [66–69]. It is possible that the increased rates of extrinsic asthma reported in the Australian Aboriginal population could similarly be due to a combination of both environmental and dietary changes.

Another alteration in diet that is thought to contribute to allergic asthma is a decrease in the consumption of fresh fruits and vegetables (FAVs), translating to lower levels of circulating antioxidants [66, 70, 71]. In RAR regions of Australia, particularly, fresh FAVs are both costly and in limited supply, again possibly contributing to the low antioxidant levels and allergic asthma seen in these individuals [22, 39, 70]. Several observational and epidemiology studies support the protective role of antioxidants in asthma and, in particular, improvements in ventilatory function [66, 72]. It is believed antioxidants help to prevent oxidative stress and damage that occurs against pulmonary epithelial cells, negatively compounded by the rapid influx of inflammatory cells and their associated mediators [72]. However, there are also recent publications arguing, paradoxically, that antioxidants *contribute* to the development of allergic asthma with the rationale that abundance leads to suppression of Th₂ responses [72]. Clearly more research is needed in this area in addition to the role that PUFAs and other dietary factors play in extrinsic asthma and, in particular, how they relate to the increasing prevalence of atopy in Australia's Indigenous population.

Food Allergy

The contemporary proinflammatory Western diet is believed to be responsible for the current rise in food allergies at a far more rapid rate than any changes in the human genome can account for [15, 35]. Globally, the following common offenders have been identified: sesame seed (used frequently in fast food), hen eggs, cow's milk, wheat, and peanut [9, 15, 73]. Of all the countries that are currently experiencing an increase in prevalence of food allergy epidemic, Australia is one of the most prominent [15].

TABLE 3. Immunological reaction types: the 4 types of immunological reactions and their associated features

Immunologic reaction type	Features
Type 1: IgE-mediated	• An immediate-type immune reaction that may be fatal due to anaphylactic shock • Diagnosed via clinical history, medical examination, allergy tests and oral food challenge
Type 2: ADCC	• Cellular cytotoxic reactions mediated by IgG and IgM • Occurs after repeated exposure to an Ag
Type 3: Ag-Ab immune complex	• IgG complex's form and become deposited in tissues resulting in pathology • Can also involve complement proteins
Type 4: Delayed-type hypersensitivity	• Cell-mediated via T cells • Occurs 2–24 hours after challenge exposure to Ag

Note. ADCC, antibody-dependant cell-mediated cytotoxicity; Ag, antigen; Ab, antibody.

Challenge-proven IgE-mediated food allergy is more prevalent among the pediatric population, with 10% of infants at 1 year of age experiencing the condition [74]. Significantly, in contrast to prior generations, these food allergies are retained into adolescence [15]. No studies could be found reporting on the epidemiology of food allergy in Indigenous populations in Australia.

At present, food allergy is defined as immune responses skewed toward Th₂-cell effects, and the production of IL-4, IL-5, and IL-13, resulting in IgE-mediated hypersensitivity [75]. Immunologically, the underlying causes are multifaceted and encompass both immediate and delayed-type reactions (Table 3). However, only approximately 5% of food allergies are caused by an immediate-type immune reaction [9]. It has been proposed that dysfunction (including damage) of the intestinal epithelium contributes to the pathophysiology of food allergy [76]. Problems with the integrity of this barrier (including immaturity due to young age) allow allergens to enter the subepithelial region and cause inappropriate immune responses [75, 76]. Tolerogenic dendritic cells are central to the pathophysiology of food allergy due to their involvement in allergic sensitization and the regulation of immune responses systemically [9, 77]. Non-IgE- or cell-mediated gastrointestinal food allergies are also being investigated and interestingly studies into food protein-induced enterocolitis syndrome document an increase in the inflammatory cytokine TNF- α [78].

The Role of Vitamins A and D

Single vitamin deficiencies can lead to severe immune system malfunction and can be especially dangerous when involved in metabolic regulation [79]. Specific studies regarding both Indigenous and non-Indigenous populations of Australia and their associated rates of vitamin deficiency are extremely limited. However, it has been reported an estimated 5% of Australians have trouble accessing food (leading to nutrient deficiency), and that this figure would be higher among Aboriginals, especially in RAR areas [79, 80]. A small-scale study demonstrated high levels of vitamin D deficiency among two Aboriginal groups in South Australia, particularly during non-summer months [81]. This is consistent with data showing that dark-skinned individuals globally are at risk of developing vitamin D deficiency [81, 82]. Of note, the results from a study of children in Western Australia demonstrated that low vitamin D levels at age 6 were a strong predictor of atopy in teenage years [83].

Sufficient levels of vitamin D can be synthesized in the skin after adequate exposure to ultraviolet B light from the sun, but dietary sources include fatty fish species [84]. In combination, a modern Western diet deficient in vitamin D-rich food, coupled with the fact that darker-skinned people require more sunlight for vitamin D synthesis and that people living in modern urban environments spend less time outdoors, leads to the prediction that vitamin D deficiencies would most likely be present in Indigenous Australian populations [22, 84, 85].

Vitamin D deficiency is associated with several medical conditions, including allergy, wheeze, reduced asthma control, and (in utero) dysfunctional development of airways [36, 86]. Additionally, it is required for the successful development and function of T reg cells [86]. This occurs via the active metabolite, $1,25(\text{OH})_2$ vitamin D_3 , which primes DCs (expressing the vitamin D receptor, VDR) to induce Forkhead-box protein 3^+ subset (Foxp3 $^+$) T reg cells [87,88]. On stimulation, Foxp3 $^+$ T reg cells secrete IL-10 and TGF- β , which helps decrease inflammation and induce tolerance, respectively [77, 89]. It has been shown that without the induction of Foxp3 $^+$ T reg cells (either due to absence or lack of stimulus) during priming of the active immune response by an allergen, an extreme exacerbation of allergic hyperresponsiveness occurs in airways [90]. There is also evidence that successful development of T reg cells is a requirement for oral tolerance to food antigens and when this is compromised there is an associated reduction in tolerance [91].

The absence of vitamin D (or problems with the VDR) can also cause an overexpression of IL-17 from CD4 $^+$ cells [92]. This is due to $1,25(\text{OH})_2$ vitamin D_3 's inhibitory effects on the differentiation of CD4 $^+$ cells into Th $_{17}$ cells, the producers of IL-17 [92]. Our understanding of IL-17's role in immunology is still in its infancy, but evidence suggests that it is involved with neutrophilic inflammation and the enhancement of Th $_2$ responses [93]. It has been shown that IL-17 is significantly present in the lungs of asthmatics. Further roles played by vitamin D are examined below in the section on gut microbiota.

Vitamin A deficiency can contribute to lymphoid tissue atrophy, cellular immunity dysfunction, and pathological changes in mucosal surfaces, and can impair IgG response to antigen [94]. Common sources rich in vitamin A include green vegetables, carrots, sweet potato, and liver. Vitamin A's transcriptionally active metabolite, retinoic acid, has important contributory effects on immune regulation with respect to allergy via the retinoic acid receptor α [77, 95, 96]. Retinoic acid (in addition to TGF- β) has recently been implicated in the induction of immune tolerance in conditions such as food allergy [77]. Post-oral antigen exposure T reg cells, including Foxp3 $^+$ T cells, develop in the gut-associated lymphoid tissue (GALT) after CD4 $^+$ T-cell differentiation [96]. The small intestine's lamina propria contain the DCs that promote the T-cell conversion and are dependent on GALT-based retinoic acid [95,96]. Furthermore, the absence of biologically active vitamin A skews cellular immunity toward a Th $_2$ -dominated response [76, 95]. Interestingly, the conversion of Th $_2$ cells into Foxp3 $^+$ T reg cells (in the airways) helps to suppress allergic asthma, showing the similarities between different allergic conditions and pathways involved [97].

Another interesting function of retinoic acid is in B-cell antibody production through the promotion of IgA-secreting B cells over IgE production [96, 98, 99]. The promotion of IgA secretion occurs when retinoic acid is synergized with DC-derived IL-5 or -6. The inhibition of IgE production is the result of more indirect biochemistry, namely that retinoic acid inhibits the CD40 $^+$ and IL-4-mediated synthesis of B-cell IgE [99,100]. Evidence suggests when the receptor for retinoic acid is antagonized, cell-mediated immune function and immediate signaling events are lost [95].

Vitamin A deficiency can also result in compromises to the mucosal barriers of the respiratory and gastrointestinal tracts, again emphasizing how important this nutrient is in immune function, allergy, and health [35, 98, 101].

Human Gut Microbiota: A Novel Approach

One of the most novel areas of research currently being pursued globally is the effects of the human microbiome, that is, the 10^{14} bacteria consisting of over 1000 species with a combined number of genes of around 3.3 million, and its effects on our physiology, including our innate and adaptive immune systems [33, 86]. Diet plays a central role in the structure and constitution of the gut microbiota, and more information is now becoming available about how these microbes interact with our body, our metabolic phenotypes (metabotypes) and the human immune system as a whole [33, 102] (Figure 1). Human gut microbiota are involved in a myriad of functions, including energy extraction from food, essential metabolite production, metabolism of otherwise indigestible food material, overall gut protection, including defence against pathogenic species, and immune system development [102–104].

No adequate studies have been conducted comparing differences in populations of gut microflora of urban and RAR Aboriginals and their Caucasian counterparts. One study reported a higher level of fecal bacteria present in the oropharynx of Aboriginal children when compared to Caucasians [105]. Another study showed that Aboriginal children frequently harbored bacteria involved in diseases such as gastroenteritis, diarrhea, and dysentery, including enterotoxigenic *Escherichia coli* (ETEC), *Salmonella*, *Campylobacter*, and *Shigella* species, which in malnourished children have previously been shown to cause extensive histological damage to the upper intestinal mucosa [106]. European studies have started to show important links between microflora and

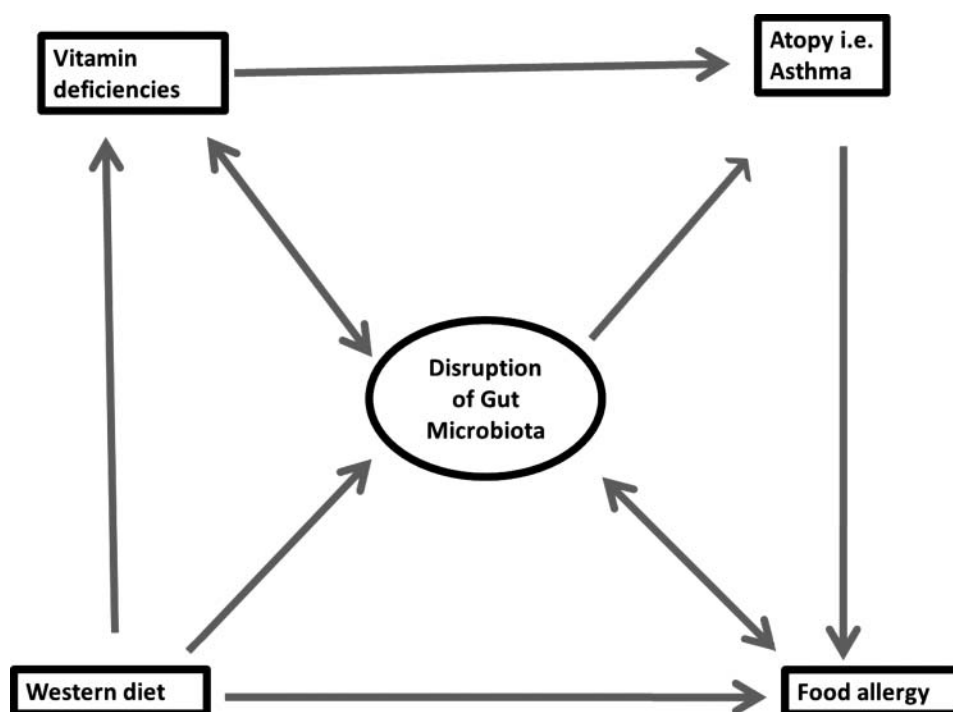


FIGURE 1. Interplay of factors relating the effect of diet on the development of allergy.

allergy, including atopic infants possessing lower levels of lactobacilli, bifidobacteria, and *Bacteroides* species and an increase in *Clostridium difficile*, experiencing higher levels of wheeze and allergic sensitization [36]. The importance of diet in relation to the immune system led to the “microflora hypothesis of allergy,” stating that important interactions between the gut microbiota and the immune system allow for immunological mechanisms that can result in tolerance or allergy [107,108]. It has been postulated that the gut microbiome is also the sensor for the development of immune tolerance in the lung, and has even been implicated in brain development and behavior [109].

The modern Western diet of high-caloric yet low-nutrient value commonly results in obesity and a drop in microbial population diversity in the gut [33]. This decrease in diversity, in combination with a lowered exposure to bacteria in the external environment, has also been associated with negative alterations in the host’s immune system, such as poorer resilience and function and the development of atopic disease [33, 36, 110]. Various immune signals assist in regulating the nexus between the immune system, nutrient metabolism, and the gut microbiota [33, 111]. Although still to be fully elucidated, the adipocyte-derived cytokine leptin is involved in appetite regulation, the maintenance of thymic output, and adjustment of the cellular immune response via dominant establishment of Th₁ over Th₂ phenotype [33, 112].

Malnutrition has severe effects on leptin serum levels, which in turn affect the immune system. This is shown in undernutrition, including acute starvation, resulting in hypoleptinemia, and also in overconsumption, leading to obesity and the subsequent development of leptin resistance [112, 113]. Both of these conditions (in addition to genetic defects in the leptin receptor) are associated with decreased cellular immunity, inflammation of the intestine, and asthma via various pathways that are yet to be fully understood [33, 114, 115]. The important link regarding the human microbiome is shown in experiments confirming that leptin levels are severely depleted in germ-free mice, and in obese leptin-deficient (*ob/ob*) mice significant differences in the taxonomic and genetic content of gut microbe populations were observed [33, 116]. For example, in obese leptin-deficient (*ob/ob*) mice, gram-negative *Bacteroidetes* species (one of the most dominant in divisions of bacteria in the human gastrointestinal system) levels dropped by 50% [36, 55, 116]. Although not yet investigated, in terms of immune modulation this could result in specific alterations in immunological functioning, such as dysfunctional maturation and development of the immune system and failure to correct T-cell deficiencies in addition to unbalanced Th-cell populations [117].

In terms of nutrients, there is evidence that vitamin D and its metabolic pathway are crucial for homeostasis in the host’s gastrointestinal system as well as for competent signaling between microbial populations and host [36]. Murine models demonstrate that an absence of the VDR leads to reduced numbers of T reg cells and chronic, mild inflammation of the gastrointestinal tract [36, 117]. The commensal gut bacteria of the host affect the distribution, transcriptional activity, and expression of epithelial cell VDR, often independently of vitamin D [36, 118]. However, the roles of various bacterial strains, obtained from differing diets, and their respective effects on VDR regulation remain to be elucidated.

Finally, one cannot talk about resident microflora and even, indeed, prebiotics (nutrients utilized by the gut bacteria) and fail to mention probiotics [119]. Probiotics are microbes that when consumed are able to resist physiochemical degradation in the gastrointestinal tract, followed by successful adherence and colonization, and culminating in positive interactions with the host, allowing for health benefits [119, 120]. There is both existing and growing evidence that these health benefits include immune system modulation and the regulation of various aspects of allergy [119, 120]. Some of

the common bacterial strains currently used as probiotics include *Bifidobacterium*, *Lactobacillus*, *Lactococcus*, *Streptococcus*, and *Enterococcus*—the first two listed being the most predominant and the latter three used only as very specific strains [120, 121]. A list of the common species of *Bifidobacterium* and *Lactobacillus* and their general effects on human health, including immune function, are reviewed in Ref. [121].

Murine models of extrinsic asthma and food allergy have shown that probiotics such as *Lactobacillus rhamnosus* GG (LGG), *L. rhamnosus*, *L. lactis* C5, and *Bifidobacterium breve* prevent allergen-specific IgE production through the modulation of cytokines, including IL-4, which contributes to airway hyperresponsiveness [120, 122, 123]. These lactic acid bacteria (LAB) have been shown to modulate IgE allergy via two differing pathways, depending on the specific strain [123]. The majority of LAB strains, including *L. casei* Shirota, induce increased serum levels of IL-12, thereby correcting the balance of Th₁:Th₂ cell populations [119, 120, 123]. A proposed secondary pathway involves induction of IL-10 secreting T reg cells (including Foxp3⁺ cells in the lungs of asthmatic mice), which serve to suppress allergen-specific IgE serum levels [123, 124]. In humans, IL-10 production as a result of LGG intake has already been established, giving further support to the idea that LAB strains in particular have the potential to alleviate allergic disease [123, 125].

Oral probiotics also promote intestinal IL-10⁺ DC populations, which aids development of local and peripheral Foxp3⁺ T reg cells (which are suppressed in allergic patients), while halting Th₂-cell-regulated inflammation [76, 126]. Murine experiments involving the administration of *B. breve* showed significant improvements in intestinal epithelial barrier function post allergy induction in addition to the previously mentioned effects [76]. Interestingly, *Bifidobacterium* could successfully translocate into intestinal tissue, but only transiently, and 5 days after introduction no *B. breve* cells were found in the host. Furthermore, increased feeding with *Bifidobacterium* did not lead to an increase in successful bacterial translocation in the mice. This suggests that continued intake and thus maintenance of the intestinal microflora are more important than acute consumption of probiotics in regards to allergy and perhaps wider health benefits.

To date, the majority of probiotics research has been on animal models due to safety concerns, ethics, control over genetic background of host, and ease of intrusive investigation [119, 127]. Human studies looking at probiotics as a treatment or prevention of allergic disease are limited, require further clarity, and have at times yielded paradoxical results [119]. In addition, few of the human studies have looked at the effects of the genetic backgrounds and epidemiologic factors of the people involved, despite host genetics and environment being important to microbial colonization [33, 86, 128, 129]. There are already indicators that the development of an individual's resident microflora via probiotics differs not only between those who are prone to develop atopy (including people from countries with higher levels of reported allergy, such as Australia), but also those who possess a unique population of gut microbes [15, 120]. It may be the unique genetic makeup of Australian Aborigines is geared to support a specific microflora that is being altered due to changes in diet and environment following westernization, resulting in associated changes in health [130, 131]. This is certainly an area that warrants further investigation.

The Hygiene Hypothesis, Parasites, and Allergy

The “hygiene hypothesis” suggests that increasing levels of “cleanliness” in combination with lack of exposure to infections, including gut parasites, endotoxins, and animals, are critical in the development of the immune system, leading to an

increased risk of asthma and other atopic diseases. However, evidence of increasing levels of asthma in remote Indigenous populations in Australia [39] and North and South American inner cities, characterized by poor housing and high levels of infections, does not support this theory [132, 133]. Epidemiological evidence, for at least some helminth species, suggests that parasite infection is associated with lowered skin prick test (SPT) responses to allergen and lowered risk of clinical asthma [134]. However, it has also been reported that effects vary with the degree of infection, with low-intensity infection stimulating specific IgE and thus SPT responses and suppression only seen in high-intensity infection [135]. Immunological mechanisms hypothesized include induction of an anti-inflammatory network mediated by dendritic cells and regulatory T cells suppressing immune responses to both helminths and allergens. The association of diet with parasite burden has been investigated only in terms of malnutrition but changes in gut microbiota composition, including intestinal epithelial barrier damage due to pathogenic parasites, suggest a complex interaction, possibly leading to intestinal allergic sensitization. Modulation of epithelial cell permeability has been demonstrated in vitro after exposure to type 2 cytokines IL-4 and IL-13 [136]. The connection between increased permeability in gut epithelial barrier and food allergy has now been established and it would be interesting to investigate linkages between gut parasite infection levels and food allergen sensitization in Indigenous populations with high parasite load.

Limitations, Recommendations, and the Future

The 2008 report on asthma rates for Australian Aboriginal people, although comprehensive, was limited by the use of multiple data sets that varied in definitions, sample populations, and regions. This causes difficulties in forming accurate conclusions on atopic health conditions affecting Aboriginal people today, and any correlations with respect to region and diet (among other variables). It is also difficult to distinguish between allergic and nonallergic asthma, which is important due to the slight differences of each condition [51].

Genetics, despite not being central to this paper's discussion, still deserves a special mention since Australian Aboriginals have such a unique genetic makeup. Genes are clearly implicated in predisposing both individuals and populations to specific diseases, including allergy [131, 137]. Recent genome-wide association studies look promising in terms of what they could reveal about the link between genes and allergy [138]. Genes that express proteins relevant to signaling pathways implicated in the molecular pathophysiology of allergic disease are continually being discovered [138]. Hopefully, studies involving the elucidation of genes that both contribute to atopy and the prevention of allergic pathology will advance in line with genome studies and inform on population genetics relevant to Indigenous Australians.

Finally, information is lacking on the effects of diet (including vitamin D and probiotic intake) among people from different genetic backgrounds and geographic location (RAR or urban) on the development of allergy [15, 33]. A deficiency in both long-term data and in vitro experimentation contributes to the lack of support for probiotics and prebiotics (found in various diets) in the treatment of allergy [36, 139]. Furthermore, there are no comprehensive studies on the relationships between microbial colonization, early-life gut microflora development, and any associated development of allergy [36]. Other areas for investigation include molecular studies on bacterial immunomodulation with respect to local and systemic allergic inflammation; what exactly constitutes a healthy microbiota (and would this differ between populations such as Indigenous and non-Indigenous people?); and how an unhealthy gut microbiota can be manipulated to confer positive health benefits [55]. Studies combining

metagenomics and gnotobiotics are seen as a potential way to help address many of the above issues [33].

CONCLUSIONS

The microbiome of the gut has a significant influence on the human immune system and the regulation of allergy. This mass collection of diverse microbial populations and genes is believed to play a crucial role in maintaining resilience against allergens and their resultant effects. Discovery of what constitutes a healthy gut microbiota and how to positively influence this via diet, prebiotics, and probiotics is yet to be fully elucidated, but there is evidence of an important interplay between host and microflora taking place in allergic disease to help skew T-cell responses toward the Th₁ phenotype and to lead to a reduction in allergic inflammation. Due to the unique genome of Aboriginal populations, it can be theorized that several factors, including type of diet, geographic location, and resident microflora, have a direct role to play in terms of the development of allergy and its pathophysiology. Studies comparing RAR and urban populations of Aboriginal people against their Caucasian counterparts in this regard would yield quite interesting results. Such studies will assist in the development of further understanding of not just Indigenous Australian health, but allergy and the immune system as a whole.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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