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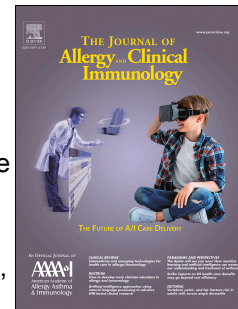
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Title: Dietary patterns in childhood and their effect on gut microbiota – an Asian perspective on atopy risk

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The prevalence of atopic disorders has risen in various parts of the world, including Asia. This increase coincides with rapid urbanization and related lifestyle changes, such as antibiotic overuse, hyper-hygienic living conditions, climate change, and air pollution. The transition from a traditional to Westernized diet is known to elicit compositional and functional shifts in gut microbiota, and is thought to underlie the pathogenesis of “Western-lifestyle” diseases in developing societies. A large cohort study involving ethnic minority Asians migrating from Southeast Asia to the United States showed that living in a

Westernized environment was associated with loss of gut microbiota diversity, native gut microbiota species and plant-fiber degrading functions.¹ These changes may be related to loss of intake of staple plant foods that are ubiquitous in a traditional Asian diet or due to an overall paucity of substrate fibers in a Westernized diet.

The effects of a traditional versus Westernized diet on gut microbiota and its link to atopic dermatitis has been described in African children.² Epidemiological evidence suggests that adherence to the traditional Mediterranean diet based on a high consumption of fruits, vegetables, fish and olive oil during pregnancy and childhood has beneficial effects on asthma and atopy in children, but results are contradictory. However, gut microbiota and metabolome studies confirm that high-level consumption of plant-based foods consistent with a Mediterranean diet is associated with increased fiber-degrading microbes and short-chain fatty acid (SCFA) production in the gut.³ Interestingly, Asian migrant children living in the UK who maintained an exclusive Asian diet were shown to have a lower risk for developing bronchial hyper-reactivity than those who adopted Westernized dietary habits.⁴ This protective effect occurred in a dose-dependent manner, consistent with the positive correlation between SCFA production and compliance level to a Mediterranean diet or diet type.³

We hypothesize that a traditional Asian diet may reduce atopy risk. Figure 1 describes the characteristics of a traditional Asian diet and possible mechanisms through which anti-allergenic benefits may be derived. Traditional Asian diets vary widely across the region depending on locally available foods (coastal versus inland), preparation/cooking methods and cultural food beliefs. However they can be generally characterized by a high intake of fruits and vegetables, whole grains, legumes, nuts, seeds, soy foods, and herbs and spices; a moderate intake of fish, poultry, eggs, healthy cooking oils, yogurt or functional foods; and a low intake of meats and sweets. Traditional household methods using a combination of heat

treatment (boiling, steaming, stir-frying), mechanical processing (pounding, soaking), fermentation, germination or malting are often employed to prepare, cook or preserve these foods. These practices not only reduce phytate content and increase nutrient bioavailability of plant-based foods, but also reduce the allergenicity of food proteins. Communal dining, eating with hands, serving food on banana leaf or in bamboo baskets are other examples of traditional Asian food cultures that promote environment microbial exposure, increase gut microbiome diversity and facilitate immune maturation (hygiene hypothesis).

Another distinct feature of traditional Asian diets is the high intake of soy and soy products (e.g. tofu, miso, and natto) compared with Mediterranean and western diets. Soy foods are a rich source of prebiotics, probiotics, non-animal protein, unsaturated fats, and a high content of polyphenols thought to have antioxidant, anti-inflammatory and anti-allergic properties. In both human and animal studies, soy consumption increased bifidobacteria and lactobacilli levels, and inhibited potentially pathogenic enterobacteria populations in the gut. Soy isoflavones genistein and daidzein have been reported to prevent peanut sensitization and allergy in murine models.⁵ Functional foods are also integral to traditional Asian diets. *Kimchi* (pickled cabbage), *dahi* (curd or yogurt), as well as *tempeh* (fermented soybean) are examples of indigenous fermented foods in Korea, India, and the Malay Archipelago, respectively, that contribute to a diverse, pre- and probiotic-enriched diet.

Data on gut microbiota profile and dietary patterns of children in Asian countries is sparse and mainly derived from Eastern, South-eastern, and South Asian populations.⁶⁻⁹ In general, an urban or Westernized diet high in animal proteins, sugar and fat is associated with a *Bacteroides*-predominant profile. In contrast, a traditional rural diet is associated with increased *Prevotella* – an ancestral fermenting bacteria adept at complex carbohydrate metabolism and SCFA production. Food allergy, specifically tree nut and peanut allergy is

related to *Bacteroides* overgrowth and inversely related to *Prevotella* whereas children with IgE-mediated cow's milk allergy have a relative abundance of *Bacteroides*.¹⁰

Microbial-derived SCFAs, particularly butyrate, have intrinsic anti-inflammatory and immunomodulatory effects against atopy. As demonstrated by the CHILD and PASTURE cohort studies, infants with high butyrate levels were less likely to develop atopic sensitization whereas in the PATCH and DIABIMMUNE studies, those with eczema had reduced butyrate levels. Dietary interventions aimed at increasing SCFA-producing microbial populations and butyrate concentration present an attractive strategy for reducing atopy risks. This can include a high consumption of butyrogenic substrates such as resistant starch, butyrate-containing foods (e.g. ghee or clarified butter used in South Asian cooking), and live biotherapeutics. In the PASTURE study, infants who consumed yogurt (which contains 0.1 g of butyrate per 100 g of yogurt) and had a high level of fecal butyrate at one year of age were found to be protected against sensitization to food and inhalant allergens at 6 years.

New standards of care for allergy prevention are emerging based on concepts advocating deliberate allergen exposure to induce immune tolerance. Recommendations include timely introduction of potentially allergenic proteins at 4–6 months of age, and dietary diversity for all infants including those at risk for developing atopy. The latter promotes gut microbial diversity and increases the availability of metabolic substrates that support the preferential growth of SCFA-producing species in the infant gut. When new foods are introduced during the complementary feeding period, the infant gut microbiota expands rapidly, which in turn triggers intense T regulatory cell generation or “weaning reaction”. A missed weaning reaction during this critical window could result in pathological imprinting of the immune system and increase host susceptibility to allergic inflammations later in life.

Current evidence derived from observational studies offer persuasive inferences to support the diet-microbiota-disease hypothesis but have inherent methodologic limitations for guiding clinical practice. Well-designed human intervention trials are needed to establish a causal relationship between diet and atopy risk, and to address the dose, timing, duration and frequency of dietary interventions. Future studies using integrative multi-omics approach are also needed, as individuals with different microbiome profiles and risk phenotypes are likely to respond differently to a dietary intervention. Better understanding of ancestral gut microbiota signatures and their relation to nutritional components and host atopy status may provide opportunities for novel interventions, including next-generation pre- and probiotic cocktails to repopulate or preserve the Asian microbiome. Until sufficient progress in precision nutrition research has been made, culturally adapted dietary strategies to modulate childhood gut microbiota may be a rational approach to mitigate atopy risks.

References

1. Vangay P, Johnson AJ, Ward TL, Al-Ghalith GA, Shields-Cutler RR, Hillmann BM, et al. US immigration westernizes the human gut microbiome. *Cell* 2018;175:962-72.e10.
2. Mahdavinia M, Rasmussen HE, Botha M, Binh Tran TD, Van den Berg JP, Sodergren E, et al. Effects of diet on the childhood gut microbiome and its implications for atopic dermatitis. *J Allergy Clin Immunol* 2019. 143:1636-7.
3. De Filippis F, Pellegrini N, Vannini L, Jeffrey IB, La Stora A, Laghi L, et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut* 2016;65:1812-21.

4. Carey OJ, Cookson JB, Britton J, Tattersfield AE. The effect of lifestyle on wheeze, atopy, and bronchial hyperreactivity in Asian and white children. *Am J Respir Crit Care Med* 1996;154:537-40.
5. Masilamani M, Wei J, Bhatt S, Paul M, Yakir S, Sampson HA. Soybean isoflavones regulate dendritic cell function and suppress allergic sensitization to peanut. *J Allergy Clin Immunol* 2011;128:1242-50.
6. Nakayama J, Watanabe K, Jiang J, Matsuda K, Chao SH, Haryono P, et al. Diversity in gut bacterial community of school-age children in Asia. *Sci Rep* 2015;5:8397. doi: 10.1038/srep08397.
7. Nakayama J, Yamamoto A, Palermo-Conde LA, Higashi K, Sonomoto K, Tan J, et al. Impact of Westernized diet on gut microbiota in children on Leyte Island. *Front Microbiol* 2017;8:197. doi: 10.3389/fmicb.2017.00197.
8. Kisuse J, La-Ongkham O, Nakphaichit M, Therdtatha P, Momoda R, Tanaka M, et al. Urban diets linked to gut microbiome and metabolome alteration in children: a comparative cross-sectional study in Thailand. *Front Microbiol* 2019;9:1345. doi: 10.3389/fmicb.2018.01345.
9. Lin A, Bik EM, Costello EK, Dethlefsen L, Haque R, Relman DA, et al. Distinct distal gut microbiome diversity and composition in healthy children from Bangladesh and the United States. *PLoS One* 2013;8:e53838. doi: 10.1371/journal.pone.0053838.
10. Berni Canani R, De Filippis F, Nocerino R, Paparo L, Di Scala C, Cosenza L, et al. Gut microbiota composition and butyrate production in children affected by non-IgE-mediated cow's milk allergy. *Sci Rep* 2018 21;8:12500. doi: 10.1038/s41598-018-30428-3.

170 Important note: References for studies cited within this article and full bibliography are
171 available upon request.

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173 **Figure legends**

174 **Figure 1. Characteristics of a traditional Asian diet and potential mechanisms for**
175 **reducing atopy risk.**

176 SCFA, short-chain fatty acid.

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