Role of dietary fiber in promoting immune health-An EAACI position paper

Carina Venter, Rosan Meyer, Matthew Greenhawt, Isabella Pali-Schöll, Bright Nwaru, Caroline Roduit, Eva Untersmayr, Karine Adel-Patient, Ioana Agache, Carlo Agostoni, et al.

Received: 21 November 2021 | Revised: 27 June 2022 | Accepted: 4 July 2022

DOI: 10.1111/all.15430

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

EAACI POSITION PAPER

Role of dietary fiber in promoting immune health—An EAACI position paper

Carina Venter[1,2] | Rosan W. Meyer[3] | Matthew Greenhawt[1,2] | Isabella Pali-Schöll[4] | Bright Nwaru[5] | Caroline Roduit[6,7] | Eva Untersmayr[8] | Karine Adel-Patient[9] | Ioana Agache[10] | Carlo Agostoni[11,12] | Cezmi A. Akdis[7,13] | Mary Feeney[14,15] | Karin Hoffmann-Sommergruber[8] | Nonhlanhla Lunjani[16,17] | Kate Grimshaw[18] | Imke Reese[19] | Peter K. Smith[20] | Milena Sokolowska[13] | Emilia Vassilopoulou[21] | Berber Vlieg-Boerstra[22,23] | Shriya Amara[24] | Jens Walter[16,25,26] | Liam O'Mahony[16,25,26]

[1]Section of Allergy and Immunology, University of Colorado School of Medicine, Aurora, Colorado, USA

[2]Children's Hospital Colorado, Aurora, Colorado, USA

[3]Imperial College, London, UK

[4]Comparative Medicine, Messerli Research Institute of the University of Veterinary Medicine Vienna, Medical University Vienna, Vienna, Austria

[5]Krefting Research Centre, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

[6]University Children's Hospital Zurich, Zurich, Switzerland

[7]Christine Kühne-Center for Allergy Research and Education, Davos, Switzerland

[8]Institute of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria

[9]Université Paris-Saclay, CEA, INRAE, UMR MTS/SPI/Laboratoire d'Immuno-Allergie Alimentaire (LIAA), INRA, CEA, Université Paris Saclay, Gif sur Yvette Cedex, France

[10]Transylvania University, Brasov, Romania

[11]Pediatric Unit, De Marchi Clinic, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy

[12]Dipartimento di Scienze Cliniche e di Comunita, Universita' degli Studi, Milan, Italy

[13]Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland

[14]Division of Asthma, Allergy and Lung Biology, Department of Paediatric Allergy, King's College London, London, UK

[15]Guy's & St Thomas' Hospital, London, UK

[16]APC Microbiome Ireland, National University of Ireland, Cork, Ireland

[17]University of Cape Town, Cape Town, South Africa

[18]Dietetic Department, Salford Royal NHS Foundation Trust, Salford, UK

[19]Private Practice for Dietary Advice and Nutrition Therapy, Munich, Germany

[20]School of Medicine, Griffith University, Southport, Australia

[21]Department of Nutritonal Sciences and Dietetics, International Hellenic University, Thessaloniki, Greece

[22]OLVG, Department of Paediatrics, Amsterdam, the Netherlands

[23]Rijnstate Hospital, Department of Paediatrics, Arnhem, The Netherlands

[24]Undergraduate, University College Los Angeles, Los Angeles, California, USA

[25]Department of Medicine, National University of Ireland, Cork, Ireland

[26]School of Microbiology, National University of Ireland, Cork, Ireland

Correspondence
Liam O'Mahony, Department of Medicine and School of Microbiology, APC Microbiome Ireland, University College Cork, Cork, Ireland.
Email: liam.omahony@ucc.ie

Abstract

Microbial metabolism of specific dietary components, such as fiber, contributes to the sophisticated inter-kingdom dialogue in the gut that maintains a stable environment with important beneficial physiological, metabolic, and immunological effects on the host. Historical changes in fiber intake may be contributing to the increase of allergic and hypersensitivity disorders as fiber-derived metabolites are evolutionarily hard-wired into the molecular circuitry governing immune cell decision-making processes. In this review, we highlight the importance of fiber as a dietary ingredient, its effects on the microbiome, its effects on immune regulation, the importance of appropriate timing of intervention to target any potential window of opportunity, and potential mechanisms for dietary fibers in the prevention and management of allergic diseases. In addition, we review the human studies examining fiber or prebiotic interventions on asthma and respiratory outcomes, allergic rhinitis, atopic dermatitis, and overall risk of atopic disorders. While exposures, interventions, and outcomes were too heterogeneous for meta-analysis, there is significant potential for using fiber in targeted manipulations of the gut microbiome and its metabolic functions in promoting immune health.

KEYWORDS
allergy, diet, fiber, nutrition, prebiotics

1 | INTRODUCTION

Recent decades have seen a rapid increase in chronic inflammatory disorders due to inappropriate or misdirected immune responses accompanied by insufficient development of immune regulatory networks. It is generally accepted that changes in environment, lifestyle, and dietary factors may play a role in the miseducation or deficient training of the immune system.[1–3] A shift away from traditional diets rich in plant-based foods to highly processed foods is thought to be particularly important for negatively affecting microbiome diversity and composition, species-specific characteristics, microbial metabolism, and immunological tolerance.[4,5] While we acknowledge that a range of nutritional factors may play a role in influencing immune function and immune regulation, in this review we will focus specifically on one dietary component—fiber.

Dietary fiber is a complex dietary component, including carbohydrate polymers and oligomers, which makes up the non-digestible components of food.[6,7] All dietary fibers resist digestion in the small bowel and pass into the large bowel intact but differ in their physiochemical characteristics (e.g., solubility, viscosity, and fermentability), which determine their functionality in the gut and to what degree they are accessible by microbes. Most soluble fibers can be fermented by the gut microbiota, partially or completely, dependent on their chemical structure. Dietary fibers can be defined on the basis of their chemical compounds, on the basis of their functional compounds, or both. Slight differences in definitions of dietary fibers exist due to the wide range of non-digestible fibers that occur in nature. The European Food Safety Authority (EFSA) defines dietary fiber as "non-digestible carbohydrates plus lignin."[8] These include non-starch polysaccharides (NSP) cellulose, hemicelluloses, pectins, hydrocolloids (i.e., gums, mucilages, and β-glucans), resistant oligosaccharides, resistant starch (consisting of physically enclosed starch, some types of raw starch granules, retrograded amylose, chemically and/or physically modified starches), and lignin associated with the dietary fiber polysaccharides (Table 1).

Prebiotics are often equated with dietary fibers, but only a subset of dietary fibers qualifies as prebiotics. Not all fibers are equally fermentable by the gut microbiota (Table 1), with considerable inter-individual variation in the potential in vivo fermentability of dietary fiber.[9–11] The term "prebiotic" was first defined by Gibson and Roberfroid over 25 years ago as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improving host health."[12] This definition has evolved to a more simplified version—"a substrate that is selectively utilized by host microorganisms conferring a health benefit."[13] The most common prebiotic fermentable fibers that have been studied for immune health benefits to date include inulin, fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), and xylooligosaccharides (XOS).[14] The most recent definition of prebiotics also allows for non-fiber substrates to be potentially classified as prebiotics.[15]

2 | THE IMPORTANCE OF FIBER AS A DIETARY COMPONENT

The evolution of the definition of prebiotics is shown in Table 2, and international dietary guidance on fiber intake is shown in Table 3. Diets rich in plant foods are those that include fruits, vegetables, whole grains, legumes, nuts, and seeds (Table 4). Such diets are

TABLE 1 Classification of dietary fibers

Category	Fiber & structure	Fermentability by the gut microbiome[9–11]	Food sources
Non-starch polysaccharides (NSP)	Cellulose (linear) β(1 → 4) linked D-glucose units	10%–30%	Grains, fruits, vegetables and nuts.
	Hemicelluloses (Branched) (a) Xylans β-(1 → 4)-linked xylose backbone (b) Mannans β-(1 → 4) linked D-mannopyranose residues ± β-(1 → 4) linked D-glucopyranose residues (c) Mixed linkage b-glucans β-(1 → 4) D-Glucopyranose separated by single β-(1 → 3) D-Glucopyranose (d) Xyloglucans β-(1 → 4)-linked D-glucopyranose with xylopyranosyl units attached	50%–70%	Cereals
	Pectins α-(1 → 4)-linked galacturonic acid	~100%	Fruit and vegetables
	Hydrocolloids, that is, gums, mucilages, β-glucans Hydrophilic polymers from multiple plant sources	~100%	Gums: plant exudates, seeds, and seaweed Mucilage: Natural gums Cereals: barley and oats, sorghum, rye, maize, triticale, wheat, and rice
Resistant oligosaccharides	Fructo-oligosaccharides (FOS) β(2 → 1) linked D-fructose residues with a terminal α(1 → 2) linked D-glucose	100%	FOS: fruits, vegetables and cereals
	Galacto-oligosaccharides (GOS) β-(1 → 6) linked galactosyl residues that terminate in a β-(1 → 4) linked glucose unit	100%	GOS: Fruit and vegetables
	Xylo-oligosaccharides (XOS) xylose residues linked through β-(1 → 4)-linkage	100%	XOS: Bamboo shoots, fruits, vegetables, milk, and honey
	Other resistant oligosaccharides)	100%	Raffinose oligosaccharides: Seeds of legumes, lentils, peas, beans, chickpeas, mallow, and mustard
Resistant starch	Physically enclosed starch (α-(1 → 4)-linked glucose monomers), some types of raw starch granules, retrograded amylose, chemically and/or physically modified starches	~100%	Whole grains, legumes, cooked and chilled pasta, potatoes and rice, and unripe bananas.
Lignin associated with the dietary fiber polysaccharides	High-molecular-weight, insoluble plant polymers, which have complex and variable structures. They are composed essentially of many methoxylated derivatives of benzene.	0%	Celery and grains

associated with improved gastrointestinal, cardiovascular, and metabolic health.[16,17] In fact, the American Gut Study showed that eating 30 plant-based foods per week was associated with the highest levels of gut microbial diversity.[18] In addition to their high fiber content, these foods also typically have a lower energy density and lower glycemic index, and contain important micronutrients, essential fatty acids, and other bioactive substances that may contribute to overall health. EFSA recommends 25 g dietary fiber per day for adults to promote adequate laxation, while recommendations for prevention of type 2 diabetes, cardiovascular disease, colorectal cancer, overweight, and obesity are higher (25–38 g/day).[19] Evidence is currently too limited to recommend any specific types of fiber, so instead a diet rich in vegetables, fruits, and whole-grain cereals is advised.[19] There is less information available to set dietary fiber recommendations in children, and current guidelines have been based on those for adults and vary according to energy requirements. This may in part be due to the difficulties faced when performing nutritional studies in this age group. EFSA suggests an intake of 2 g/MJ (megajoules) is considered adequate for normal laxation in children from the age of 1 year. There are no guidelines for fiber intake below 1 year of age. As research advances, recommendations should expand to include individual fibers and consider the effects and physiochemical properties of specific fiber-rich foods in combination with other supplements.

3 | FIBER EFFECTS ON THE MICROBIOME

Certain fibers, also termed microbiota-accessible carbohydrates (MACs), are an essential food source for the microbiome in that they provide resources for microbial growth and metabolism. They are central to food-webs in the gut microbiota established through cross-feeding, and reduced fiber intake has been shown to be associated with the loss of ancestral microbes.[5] Overall, species diversity and richness have been shown to be reduced by about one third in North Americans compared to Malawians or Amerindians, which might be due in part to changes in dietary fiber consumption.[20] A high fat/low fiber diet and obesity have been associated with negative

TABLE 2 Evolution of the definition of prebiotics

Reference	Year	Definition
Gibson GR & Robefroid[11]	1995	Non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria already resident in the colon
Reid et al.[12]	2003	Non-digestible substances that provide a beneficial physiologic effect on the host by selectively stimulating the favorable growth or activity of a limited number of indigenous bacteria.
Gibson et al.[13]	2004	selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well-being and health
Robefroid et al.[14]	2007	A selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora, that confer benefits upon host well-being and health.
Pineiro et al.[15]	2008	A non-viable food component that confers a health benefit on the host associated with modulation of the microbiota
Gibson et al.[16]	2010	Dietary prebiotics' as "a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health
Bindels et al.[17]	2015	Non-digestible compound that, through its metabolization by microorganisms in the gut, modulates the composition and/or activity of the gut microbiota, thus, conferring a beneficial physiological effect on the host.
Gibson et al.[18]	2017	A substrate that is selectively utilized by host microorganisms conferring a health benefit

TABLE 3 Dietary fiber recommendations

Region/Country	Dietary fiber (g/day) adults	Dietary fiber (g/day) children
EU EFSA 2010	25 g/day	2 g/MJ from 1 year
UK SACN 2015	30 g/day	2–5 years: 15 g/day 5–11 years: 20 g/day 11–16 years: 25 g/day
USA IOM, 2020	Men 19–30: 34 g/day 50 years: 31 g/day >50 years: 28 g/day Women 19–30: 28 g/day 31–50 years: 25 g/day >50 years: 22 g/day	Male/Female: 2–3 years: 14 g/day Male: 4–8 years: 20 g/day 9–13 years: 25 g/day 14–18 years: 31 g/day Female: 4–8 years: 17 g/day 9–13 years: 22 g/day 14–18 years: 25 g/day

TABLE 4 Sample menu of how to meet recommended fiber intake

Meal	Foods	Portion size (g)	Fiber (g)
Breakfast	Muesli	40 g	3.1 g
	Dairy/non-dairy milk	120 mL	0.6 g
	Strawberries	36 g	1.4 g
Snack			
	Small handful of nuts	28 g	1.3 g
	1 apple	100 g	1.2 g
Lunch			
	1 slice whole meal bread	40 g	2.8 g
	Roasted squash &	60 g	1.2 g
	Lentil salad	80 g	4.1 g
	Pumpkin seeds	16 g	1.1 g
	Goat's cheese	35 g	-
	Pear	75 g	2.0 g
Evening meal			
	Vegetable curry	200 g	4.8 g
	Wholegrain rice	180 g	2.7 g
	Greek yoghurt	90 g	-
	Nectarine	150 g	2.4 g
	Flaked almonds	16 g	1.6 g
		Total	30.4 g

alterations in gut microbiota composition and metabolic activity.[21,22] In contrast, a recent meta-analysis confirmed that consumption of high fiber foods such as nuts significantly increased levels of important microbial taxa including *Clostridium*, *Dialister*, *Lachnospira*, and *Roseburia*.[23] Specific fibers may induce distinct responses, as was recently shown for arabinoxylan that reduces LDL levels, while in the same study long-chain inulin increased *Bifidobacterium* levels.[24] In addition, overall dietary patterns might be more important than individual types of fiber in supporting specific taxa as suggested by studies linking *Faecalibacterium prausnitzii* and *Roseburia* abundances with increased adherence to a Mediterranean diet (containing high levels of fiber).[25–27]

The degradation of dietary fibers requires specific CAZymes (carbohydrate-active enzymes), which are encoded in the genomes of specific bacterial strains.[28,29] While the human genome encodes potentially up to 17 glycoside hydrolases, thousands of gut microbiota genes that encode glycoside hydrolases, polysaccharide lyases, glycosyltransferases, and carbohydrate esterases have been described, demonstrating the indispensable role of the gut microbiota in fiber metabolism.[28,30] Members of the Bacteroidetes phylum (in particular *Prevotella copri*) seem to possess a greater number of CAZymes compared to other phyla, suggesting a increased capability to ferment a wider range of substrates.[28,31] Given that specific CAZyme gene clusters target discrete structures within dietary fibers, therefore specific subsets of microbes are supported by different types of dietary fibers, which highlights the potential for using selected fiber structures to achieve targeted functional, metabolic, and perhaps immunological outcomes.[32,33] However, one recent study showed that high fiber consumption on its own did not result in all the expected microbiota and immune benefits as participants microbiota seemed unable to process the increased amount of fiber, suggesting the extinction of the bacterial strains required to process non-digestible carbohydrates into immune modulatory metabolites in certain industrialized human microbiomes.[34]

4 | FIBER EFFECTS ON THE IMMUNE SYSTEM

Dietary fibers can have direct and indirect effects on the host immune system.[35] Before being fermented by microbes in the colon, dietary fibers can have a substantial impact on the intestine via modulation of intestinal barrier function and immune responses (Figure 1). GOS, inulins, pectins, and β-galactomannan have been

shown to support a functional intestinal epithelial barrier by modulation of tight junction protein assembly, goblet cell activation and function, regulation of epithelial cell growth and glycocalyx maturation.[36–41] In addition, in vitro studies suggest that fibers including inulin, GOS, FOS, and arabinoxylan hydrolysates can modulate epithelial cell, macrophage and dendritic cell cytokine and chemokine secretion, in part mediated by activation of peroxisome proliferator-activated receptor gamma (PPARγ).[42–46] An additional mechanism for direct fiber effects on immune cells is their activation of pattern recognition receptors (PRRs) such as C-type lectin receptors (CLRs, e.g., β-glucans), galectins, or Toll-like receptors (mainly TLR-2 and TLR-4, e.g., GOS and FOS) on epithelial cells and cells of the innate immune system.[47–49] Fibers may also inhibit PRRs activation such as was shown for pectin, which blocked TLR-2 induced cytokine secretion.[50] However, there are significant technical challenges in discerning contamination-mediated TLR activation from true fiber subunit-mediated TLR activation.

Following microbial fermentation, a wide range of potential immunological metabolites are produced. The best-described metabolites are short-chain fatty acids (SCFAs), which include acetate, propionate, and butyrate (Figure 2).[51] A wide range of microbes can generate SCFAs, but the most frequently described are *Clostridium*, *Bacteroides*, *Bifidobacterium*, *Prevotella*, and *Ruminococcus*. Distinct enzymatic pathways (indicated in Figure 2) are responsible for the generation of each SCFA, and some microbes can synthesize butyrate from acetate and lactate.[52] SCFAs exert effects on the host immune system via binding to G protein-coupled receptors (GPCRs) such as GPR41, GPR43, and GPR109A, via epigenetic modifications that inhibit histone deacetylase (HDAC) activity, and most recently butyrate has been described as an aryl hydrocarbon receptor (AhR) ligand.[53,54] SCFAs are potent immunomodulators that promote IL-10 secretion by dendritic cells and lymphocytes, influence Treg numbers and effectiveness, influence bone marrow hematopoiesis, reduce effector T cell activity, improve epithelial barrier, support IgA secretion by B lymphocytes, inhibit mast cell degranulation, and modulate ILC activation.[55–62] IL-10-producing regulatory B cells (B10 cells) can be directly promoted by acetate following its conversion into acetyl-CoA, which mediated B10 cell differentiation through fueling the TCA cycle and OXPHOS and protein acetylation.[63] Fiber consumption or SCFA administration in experimental models protects against colitis, inflammatory arthritis, respiratory syncytial virus infection, allergic airway inflammation, and food allergy.[64–66] Epigenetic mechanisms seem particularly important for the induction of T regulatory cells in the gut as butyrate enhances histone acetylation of the Foxp3 promoter thereby driving Treg development.[67,68] Consumption of fruits and vegetables during the first year of life is associated with increased levels of fecal butyrate, and those children with the highest fecal levels of butyrate and propionate were less likely to develop allergies and asthma later in life.[64] Consumption of a similar dietary pattern during pregnancy

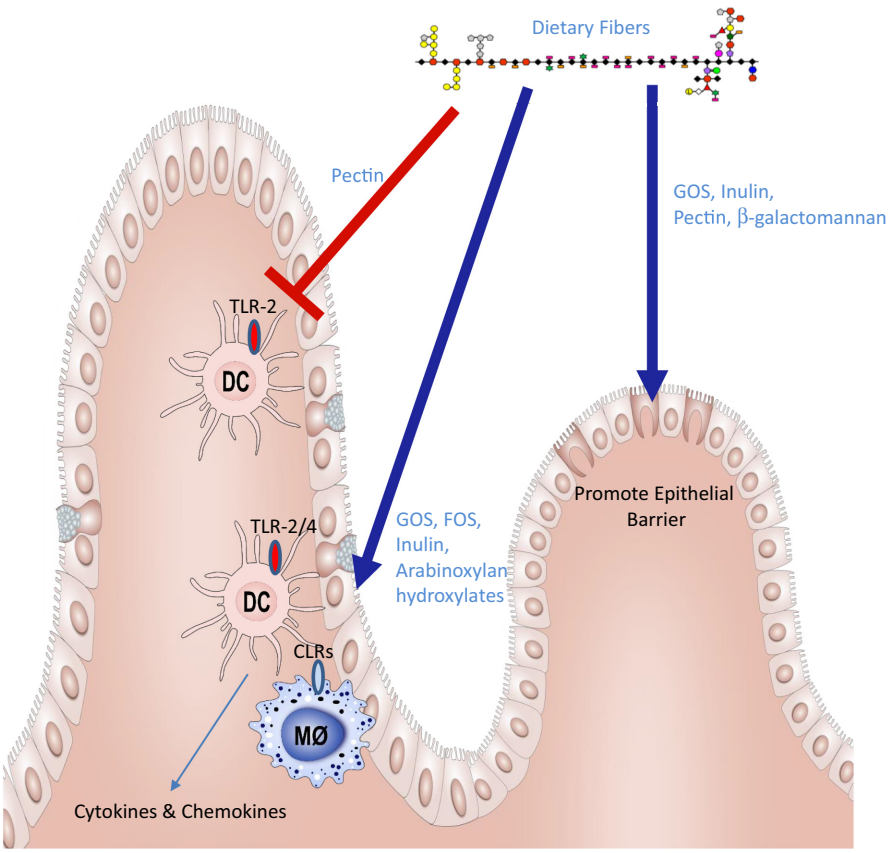

FIGURE 1 Direct effects of fibers on epithelial and immune cells. Dietary fibers such as GOS, inulins, pectins, and β-galactomannan have been shown to support a functional intestinal epithelial barrier. In addition, in vitro studies suggest that fibers including inulin, GOS, FOS, and arabinoxylan hydrolysates can modulate epithelial cell, macrophage and dendritic cell cytokine and chemokine secretion, potentially via their activation of C-type lectin receptors (CLRs) or Toll-like receptors (TLR-2 and TLR-4). In contrast, fibers such as pectin may also inhibit TLR-2-induced cytokine secretion.

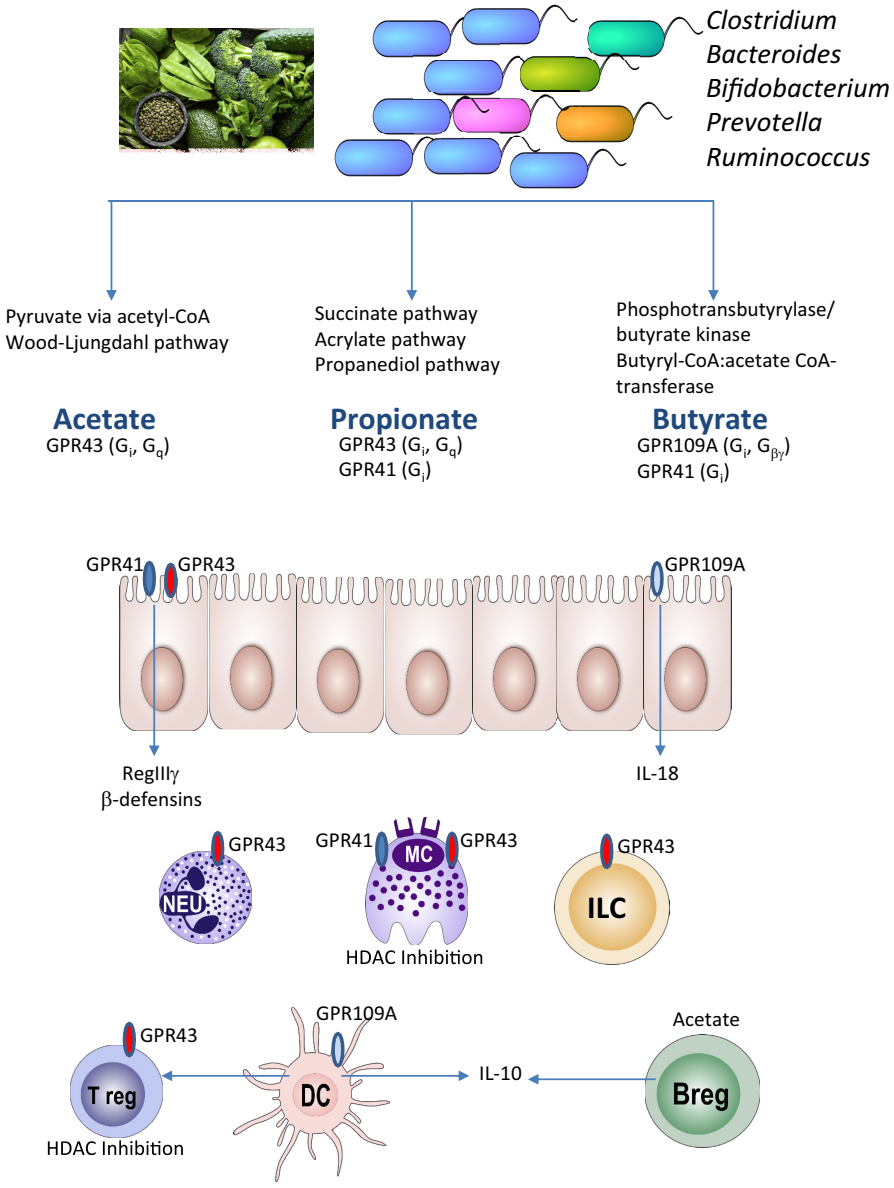

FIGURE 2 Mechanisms of SCFAs generation and interactions with the immune system. Fermentation of dietary fibers by specific microbial species (examples are illustrated) generates acetate, propionate, and butyrate via distinct enzymatic pathways (illustrated for each metabolite). The G protein-coupled receptor that binds each metabolite with high affinity is illustrated, and the Galpha signaling subunit is indicated for each receptor. Immune cell subsets that express SCFA receptors, or are impacted due the HDAC inhibition, include epithelial cells, dendritic cells, Tregs, neutrophils, mast cells, and ILCs.

was also associated with reduced risk of allergy in the offspring.[69] Importantly, adults who more regularly consumed plant-based or pescatarian diets had a lower risk of developing severe COVID-19.[70–72] While it is not known if the fiber component of the plant diet was responsible for the protective association, the microbiota composition associated with severe COVID-19 does suggest a lack of fiber consumption in those individuals that correlates with hyper-inflammatory responses and reduced barrier function.[73,74]

5 | SYSTEMATIC REVIEW: IMPORTANCE OF FIBERS FOR ALLERGY PREVENTION AND TREATMENT

Several guidelines and systematic reviews have previously examined the role of both fiber and prebiotic supplementation with respect to allergy outcomes. An earlier review in 2015 by Orel et al. concluded that "the strongest evidence on beneficial effects of prebiotics in children exists in relation to the fight against constipation, poor weight-gain in preterm infants and prevention of eczema in atopic children."[75] The World Allergy Organization (WAO) GLAD-P document stated that prebiotics could be added to the diet of not-exclusively breastfed infants, both at high and at low risk for developing allergy, however, not in exclusively breastfed infants. This is a conditional recommendation with very low certainty of evidence.[76] The supporting GRADE analysis for this document regarding the use of prebiotics given to infants stated there is "a possible effect of prebiotic supplementation in infants on the reduction in the risk of asthma or wheezing," in that prebiotics might reduce the risk of recurrent wheezing in infants, but this had a very low level of certainty due to "risk of bias, indirectness of the evidence, and imprecision due to low number of events of the estimated effect."[77] The Philippine guidelines on dietary primary prevention state that prebiotics are not recommended to prevent allergic diseases (with a strong recommendation level due to low-quality

evidence).[78] A systematic review from the United Kingdom on dietary recommendations for infants and pregnant or lactating mothers also reports that there is no clear evidence that prebiotic supplementation reduces eczema at age ≤4 years (RR 0.75; 95% CI 0.56 ± 1.01; I^2 = 57%) and no association at age 5–14 years when given to infants in infant formula.[79] This was followed by a systematic review from Skorka et al.[80] who noted no difference on allergy outcomes between GOS-supplemented and unsupplemented infant formula in one study, while an additional study examining GOS/FOS-supplemented formula showed a significant reduction in allergic reactions to food (3/62 vs. 9/53, respectively; RR 0.28; 95% CI 0.09, 0.9), allergic reactions to cows' milk protein (2/62 vs. 8/53, respectively; RR 0.2; 95% CI 0.05, 0.84), atopic dermatitis (3/62 vs. 9/53, respectively; RR 0.28; 95% CI 0.09, 0.9), and gastrointestinal symptoms of food allergy (2/62 vs. 7/53, respectively; RR 0.24; 95% CI 0.06, 0.98).[81,82] Lastly, a systematic review supporting the new EAACI food allergy prevention guidelines noted little to no effect for the role of prebiotics when administered to infants, though also stated that the evidence for this is very limited.[83]

6 | NARRATIVE REVIEW OF A SYSTEMATIC SEARCH

For the purposes of this review, we focused on studies published during the last 5 years (search time frame June 2015 to 20 November 2020) as before that time point several concise reviews and guidelines were published. In our search, we included observational epidemiological studies and clinical trials/intervention studies with application of dietary fiber and/or prebiotics to prevent or treat allergic diseases. Search terms are provided in Table S1. Based on these, 542 papers (235 from Pubmed and 307 from EMBASE) were retrieved. After removal of duplicates, 512 papers remained. Finally, after abstract and full-text screening, we identified 16 studies that involved either dietary prebiotic (n = 8) or fiber (n = 8) intake and measured allergy-relevant outcomes (Tables S2 and S3). Exposures, interventions, and outcomes were deemed to be too heterogeneous with respect to prebiotic/fiber type and assessment of the outcome to attempt to pool the data for meta-analysis, so results are summarized as a narrative systematic review only.

6.1 | Asthma/respiratory outcomes

We identified seven studies that involved either dietary prebiotic (n = 1) or fiber (n = 6) intake in three interventional studies and four observational cohort studies detailing an association with asthma/respiratory outcomes.

6.1.1 | Fiber

In a prospective observational study, Andrianasolo et al.[84] studied multiple types of dietary fiber intake in association with reported asthma control (assessed at 6 months longitudinal intervals) as indicated by the Asthma Symptom Score and the Asthma Control Test (ACT) score. They noted that higher quintiles of dietary fiber intake (total, soluble, insoluble fibers from cereals, fruit, and seeds) were associated with lower Asthma Symptom Score (0.73, 95% CI 0.67–0.79 in women; and 0.63, 95% CI 0.55–0.73 in men, both p < 0.001) compared to participants in the lowest quintile of total dietary fiber intake, indicating that higher fiber intake was associated with fewer reported asthma symptoms. Higher total fiber intake, mostly insoluble fiber and fiber from cereals were also associated with lower odds of an ACT score indicating impairment (OR 0.72, 0.55–0.95, p = 0.01 for women, OR 0.45, 0.26–0.79, p = 0.01 for men). In an unblinded randomized controlled trial, Bseikri et al.[85] noted no overall association between consumption of a high fiber nutritional supplement bar (Children's Hospital Oakland Research Institute-bar; CHORI-bar) and pulmonary function testing, ACT score and Pediatric Quality of Life Inventory–Asthma Module (PedsQoL Am) score, although they did note that among treatment-compliant subjects with non-eosinophilic asthma, 8 weeks of CHORI-bar consumption was associated with increased forced vital capacity (FVC), forced expiratory volume for 1 s (FEV-1), and forced expiratory flow between 25% and 75% of FVC (FEF-25-75). In a 3-way cross-over randomized controlled trial, McLoughlin et al.[86] noted that a 7-day trial of inulin (12 g per day) supplementation (interventional setting) was associated with improved Asthma Control Questionnaire score exceeding the minimal important difference, though not associated with objective parameters of improved lung function, but they noted a subgroup effect among those (n = 7) with the poorest asthma control in that the inulin supplementation was associated with decreased eosinophilic airway inflammation, and better overall control among those with eosinophilic versus non-eosinophilic asthma. In a cross-sectional observational study, Saeed et al.[87] noted an association between low dietary fiber intake and increased odds of reported asthma among US respondents on the National Health and Nutrition Examination survey (NHANES) survey. They noted increased odds of asthma with lower fiber intake (lowest vs. highest reported quartile, OR, 1.4; 95% CI 1.0–1.8; p = 0.027) with significant interactions between fiber and both sex and race/ethnicity, in particular among women and non-Hispanic white adults. Lowest quartile fiber intake was associated with increased odds of reported wheeze (OR, 1.3; 95% CI, 1.0–1.6; p = 0.018) and cough (OR, 1.7; 95% CI, 1.2–2.3; p = 0.002).

Two Australian studies looked at the effects of fiber during pregnancy. In a cross-sectional retrospective nested cohort study, Grieger et al.[88] noted that, after adjusting for total energy intake, pregnant women with uncontrolled asthma had higher intakes of fiber (OR 1.07, 1.03–1.13, p = 0.003). In an observational study of 639 maternal–infant pairs, Pretorius et al.[89] noted that higher reported maternal dietary intake of resistant starch was associated with reduced odds of doctor-diagnosed wheezing in the infant (aOR 0.68 (95% CI 0.49–0.95, p = 0.02)).

Overall, there is some evidence that a higher intake of dietary fiber (soluble or insoluble) may have potential protective effects on respiratory symptoms. However, the majority of the studies reviewed were small observational studies that did not clearly label the

type of fiber ingested, which limits their interpretation and extrapolation. Further prospective intervention studies are needed to better define the effects of fiber consumption on respiratory outcomes.

6.1.2 | Prebiotics

In adult asthmatic patients, a randomized, double-blind, placebo-controlled, cross-over interventional design study by Williams et al. examined the effects of 3 weeks supplementation with 5.5 g/day Bimuno-galacto-oligosaccharide (B-GOS). Supplementation with this prebiotic reduced the severity of hyperpnoea-induced bronchoconstriction (HIB, a surrogate for exercise-induced bronchoconstriction), as well as concomitant markers of airway inflammation.[90] Recipients displayed a 40% improvement in forced expiratory volume in 1 s (FEV1) decline after eucapnic voluntary hyperpnoea (EVH), and B-GOS supplementation reduced baseline concentrations of CCL17, CRP and TNF-α as well as EVH-induced increase in TNF-α.

Prebiotic supplementation to asthma patients seems to have a positive effect on exercise-induced bronchoconstriction and accompanying inflammation markers; however, as this was only a single intervention study with this design, an overall recommendation cannot be made.

6.2 | Allergic rhinitis and pollen sensitization

We identified 1 intervention study using fiber supplements in the form of a fermented beer and 1 open-label study investigating a prebiotic.

6.2.1 | Fiber

In a small single-blinded randomized controlled trial, Derakhshan et al.[91] studied the effect of 15 mg dried Ma-al-Shaheer (a traditional Iranian medicine with a formulation based on barley, *Hordeum vulgare*) versus 60 mg fexofenadine (anti-histamine) twice daily in adults with allergic rhinitis (AR) for 21 days. AR control was improved in both groups ($p < 0.001$) and symptoms were significantly reduced in both groups, although slightly better for nasal congestion, post-nasal drip, and headache among those receiving the Ma-al-Shaeer treatment.

6.2.2 | Prebiotics

In an open-label and non-controlled intervention study, atopic adults receiving the prebiotic lactosucrose (3.2 g/day for 52 weeks) had significantly decreased serum IgE levels (especially to pollen allergens) as well as allergy symptoms at the end of the study period.[92]

Both studies, while hinting at some potential effects of both fiber and prebiotics on allergic rhinitis outcomes, are limited by small patient numbers and poor study design. Larger and better-designed interventional placebo-controlled studies are needed to clarify potential benefits.

6.3 | Eczema and atopic dermatitis

We identified six studies that examined either dietary prebiotic ($n = 4$) or fiber ($n = 2$) intake in four interventional studies and 2 observational cohort studies.

6.3.1 | Fiber

For fiber, in a retrospective cross-sectional case–control study, Matano et al.[93] noted that in Japanese adults on antihistamines with poor control of their chronic urticaria, total fiber intake was not significantly associated with Urticaria Control Test (UCT) score, although urticaria patients had significantly higher fiber intake than controls ($p = 0.01$). The aforementioned study by Pretorius et al.[89] found that higher maternal intakes of resistant starch were associated with higher odds of parent-reported eczema (aOR 1.27 95% CI 1.09, 1.49, $p < 0.01$), doctor-diagnosed eczema (aOR 1.19, 95% CI 1.01, 1.41, $p = 0.04$), and doctor-diagnosed eczema in non-sensitized infants (aOR 1.29, 95% CI 1.06, 1.57, $p = 0.01$). Higher maternal intake of fiber from green vegetables was associated with higher odds of doctor-diagnosed eczema in the infant (aOR 1.32, 95% CI 1.06, 1.64, $p = 0.01$) and also in non-sensitized infants (aOR 1.36, 95% CI 1.04, 1.79, $p = 0.03$).

6.3.2 | Prebiotics

For prebiotics, Bozenky et al.[94] performed an interventional randomized controlled trial in 6–8 weeks old high-risk infants (family history of allergy in first-grade relatives), who were given a hypoallergenic formula, either supplemented with or without 0.5 g/100 mL of galacto-oligosaccharides. They noted a decreased, but not statistically significant, SCORAD score in both groups. Boyle et al.[95] showed in an international multi-center intervention study that in high-risk infants, partially hydrolyzed whey protein formula (pHF-OS) supplemented with neutral short-chain galacto-oligosaccharides (scGOS), long-chain fructo-oligosaccharides (lcFOS), and pectin-derived acidic OS (pAOS) (vs the same formula without the prebiotics) did not prevent eczema in the first year of life, even though the prebiotic containing formula modified the fecal microbiota in terms of taxonomical composition and metabolic activity.[96] In the PIPA intervention study (Prebiotics in the Prevention of Atopy), galacto-oligosaccharide/polydextrose (GOS/PDX)-supplemented formula showed no significant difference in the cumulative incidence of

eczema in the first year of life in high-risk infants compared to standard formula and breastfeeding.[97] Lastly, in an interventional trial daily administration of kestose, the smallest FOS, for 6 weeks in 2- to 5-year-olds, was significantly correlated with higher fecal *F. prausnitzii* levels and an improvement in SCORAD severity scores (rs = 0.52, $p = 0.04$).[98]

While the number of studies is limited, results to date indicate that prebiotics given to high-risk infants did not prevent development of eczema during the first year of life.

6.4 | Food allergy

No recent studies were identified that focused on the effect of fiber or prebiotics on food allergy.

6.5 | Overall risk of atopic disorders

We identified 2 interventional studies of prebiotic supplementation in healthy infants reporting on general allergic outcomes. No difference in allergic outcomes at 5 years of age was noted in an intervention study among healthy infants given either non-hydrolyzed cow milk-based formula supplemented with neutral sc-GOS, lcFOS, and pAOS, and compared to non-supplemented formula or breastfed children before the age of 8 weeks of life.[99] However, healthy daycare children aged between 1 and 4 years given a cow's milk-based beverage (CMBB) supplemented in an intervention study with docosahexaenoic acid, polydextrose, GOS, and yeast β-glucan, and additionally fortified with micronutrients (zinc, vitamin A, iron), 3 times/day for 28 weeks had fewer episodes of allergic manifestations in the skin and the respiratory tract, including allergic rhinitis or conjunctivitis, wheezing, allergic cough, eczema, and urticaria (HR 0.64; CI 95% 0.47, 0.89; $p = 0.007$).[100]

For the overall risk of atopic diseases, a positive effect for a highly supplemented (DHA, GOS, prebiotics, micronutrients) beverage was found.

7 | RECOMMENDATIONS FOR FUTURE STUDIES

- Data on prebiotic studies during pregnancy have not yet been reported, with only two fiber intervention studies during pregnancy available—this early window of opportunity for allergy prevention needs to be better explored using intervention trials.
- Pre-screening of trial participant's microbiota composition should be encouraged to facilitate precision targeting of specific selected fibers to support the health-promoting taxa (e.g., butyrate-producing microbes) already present in that specific individual.
- Trial subjects should be stratified according to their pre-trial dietary habits, including their level and diversity of fiber consumption.
- Combination of prebiotics with appropriately chosen probiotics may be required for maximal benefits, particularly in those that already lack microbes with the appropriate enzymatic machinery to utilize the administered prebiotic.
- Studies focussed on overall dietary patterns incorporating diverse fiber types and sources may be more effective that individual fibers in managing allergy risk and symptoms.
- Dosing of specific fiber types should be carefully considered especially with regard to potential negative metabolic effects.
- Longitudinal studies with a cross-over design may be particularly important to elucidate the cause-and-effect relationship between fiber intake, microbiota metabolism, and immune system dysfunction.
- Metabolites generated by microbial fermentation of dietary fibers (e.g., SCFAs) may be examined as novel therapeutic agents or immunotherapy adjuvants.

8 | SUMMARY AND CONCLUDING REMARKS

In summary, fibers are essential components of a healthy diet with multiple health benefits, and fiber intake has decreased at the same time as allergy rates have increased. There are a wide variety of fiber types, and specific fibers may contribute to maintaining a tolerogenic mucosal environment and may protect against allergic disorders. However, the optimal prevention or treatment strategies involving fibers in humans have yet to be defined. One mechanism by which fiber impacts the immune system is dependent on microbial fermentation and secretion of bioactive metabolites. Thus, fiber supplementation alone may not be sufficient and simultaneous replacement of missing microbes may be required for optimal benefits to be observed. Given the varied functional properties of different fiber types, it is unlikely that one type of fiber will provide all immune-relevant signals, and regular consumption of diverse fiber types may be superior to supplementation with individual fibers, which is consistent with our previous recommendations regarding the importance of dietary diversity in general for allergy prevention.[101] However, as our understanding progresses on the role and mechanisms mediating specific fiber-microbiota-immune interactions, there is significant potential for using fiber in targeted manipulations of the gut microbiome and its metabolic functions in promoting immune health. We suggest that the current classification of different dietary fiber types would benefit by being updated to include their specific immune functional properties, such as promotion of the epithelial barrier, induction of T regulatory cells, prevention of T_H2 polarization, and inhibition of mast cell degranulation. Overall, fiber diversity may be more important immunologically than any single individual fiber type. Of particular importance to understand is the potential relationship between timing and fiber effects on the immune system, especially in early life where there is a critical window of opportunity to influence the development of immune regulatory networks. However, there are many unique challenges

and difficulties in performing nutrition studies to provide evidence-based recommendations (e.g., method of measuring dietary intake, specific type of fiber being administered), and these will need to be acknowledged and accounted for in future studies. In addition, it was recently suggested that microbiome-focused endpoints should be embedded within all aspects of nutrition science to strengthen the evidence base for dietary guidelines.[102] Notwithstanding these limitations, there are many clinical studies underway examining the in vivo effects of fiber consumption, which will hopefully address some of the current knowledge gaps.

We also need to be aware of potentially inconsistent fiber effects across different disease endotypes, which depends on the distinct pathophysiological mechanisms in operation for the given endotype. This is of particular importance in studying heterogeneous diseases like allergic diseases and asthma and highlights the need for sufficiently powered studies. Deciphering the molecular alphabet that underpins this cellular dialogue is a significant challenge, but one that once overcome will yield the critical insights needed to prevent and treat allergic disorders in the 21st century. Future research on fiber–microbe–host interactions should be strongly encouraged as these discoveries will provide fundamental knowledge on the molecular communication networks that underpin life as a multicellular metacommunity and will progress our appreciation for the principle of biological diversity as a driver of physiological resilience and immune tolerance.

AUTHOR CONTRIBUTION

CV and LOM lead the manuscript writing. RM and CV wrote the sections on dietary fiber classification. IPS and MG lead the section on the RCTs. IPS, MG, SA, MF, and IR extracted the data for the supplementary Tables S1, S2, S3. BN performed the searches. CR, EU, IA, KHS, NJ, PKS, MS, JS, and LOM wrote the section on immunology and microbiome. CA, IR, and KAP wrote the section on prebiotics. MF, KG, BV, and EM wrote the section on dietary intake. CA, CV, and LOM reviewed the overall paper.

FUNDING INFORMATION

None.

ACKNOWLEDGEMENT

Open access funding provided by IReL.

CONFLICT OF INTEREST

Carina Venter reports personal fees from Danone, personal fees from NNI, personal fees from Abbot, grants and personal fees from Reckitt, grants from Peanut board, personal fees from Before brands, personal fees from Else nutrition, personal fees from Sifter, outside the submitted work; Berber Vlieg-Boerstra BVB reports personal fees from Marfo Food Group, Lelystad, The Netherlands, personal fees from Nestlë, grants from Nutricia Research, speaking support from Nutricia, Abbott and Nestle outside the submitted work; Rosan Meyer reports personal fees from Nestle, grants and personal fees from Nutricia/Danone, personal fees from Mead Johnson, personal fees and other from Abbott, outside the submitted work. Liam O'Mahony received research grants from GSK and Chiesi, speaker support from Nestle, Nutricia, Reckitt, and Abbott, consultant to Precision Biotics. CA received Research grants from Allergopharma, Idorsia, Swiss National Science Foundation, Christine Kühne-Center for Allergy Research and Education, European Commission's Horison's 2020 Framework Programme "CURE," Novartis Research Institutes and Astra Zeneca. Took part in the advisory board and received research grants from Glaxo Smith-Kline, Sanofi/Regeneron, Scibase, Novartis. He is the Editor-in-Chief of Allergy. Dr. Pali-Schöll reports personal fees from Bencard Allergie GmbH outside the submitted work. Peter Smith declares that he has been paid an honorarium for working on the Nestle Nutrition Institute advisory board. He also has received honorarium and/or speakers fees for Viatris, GSK, AZ, Sanofi, Mundipharama, Nutricia. He also has researcher-initiated funding from Viatris, GSK, and Sanofi. Ioana Agache is Associate Editor Allergy and Clinical and Translational allergy. Matthew Greenhawt is a consultant for Aquestive; is a member of physician/medical advisory boards for DBV Technologies, Sanofi/Regeneron, Genentech, Nutricia, Novartis, Acquestive, Allergy Therapeutics, ALK-Abello, AstraZeneca, Allergenis, and Prota; is a member of the scientific advisory council for the National Peanut Board; is a member of the Brighton Collaboration Criteria Vaccine Anaphylaxis 2.0 working group; is the senior associate editor for the Annals of Allergy, Asthma, and Immunology, and is member of the Joint Taskforce on Allergy Practice Parameters. He has received honorarium for lectures from ImSci, MedLearningGroup, the Allergy and Asthma Foundation of America, The Intermountain West Allergy Society, the Wisconsin Allergy Society, the Los Angeles Society of Allergy and Immunology, the Northern Califorina Society for Allergy and Immunology, and the Candian Society for Allergy and Clinical Immunology. Imke Reese reports personal fees from ALK-Abello, personal fees from Beiersdorf Dermo Medical GmbH, personal fees from Nestlé Deutschland GmbH, personal fees from Nutricia Milupa GmbH, personal fees from Sanomega GmbH, outside the submitted work; Milena Sokolowska reports grants from Swiss National Science Foundation, grants from GSK, outside the submitted work. Kate Grimshaw received personal fees/honorarium for work outside the submitted work from Abbott, Nestle, and Danone personal fees/honorarium for work outside the submitted work from Abbott, Nestle and Danone. The other authors have not conflict to declare (CR, CA, KA-P, JW, MF, BN, LJ, EU, KH-S, EV, SA).

ORCID

Carina Venter https://orcid.org/0000-0002-7473-5355
Rosan W. Meyer https://orcid.org/0000-0002-5710-5570
Matthew Greenhawt https://orcid.org/0000-0002-2365-9372
Isabella Pali-Schöll https://orcid.org/0000-0003-2089-6011
Bright Nwaru https://orcid.org/0000-0002-2876-6089
Caroline Roduit https://orcid.org/0000-0002-5988-0570

Eva Untersmayr https://orcid.org/0000-0002-1963-499X
Karine Adel-Patient https://orcid.org/0000-0002-2242-0626
Ioana Agache https://orcid.org/0000-0001-7994-364X
Cezmi A. Akdis https://orcid.org/0000-0001-8020-019X
Imke Reese https://orcid.org/0000-0001-8191-4020
Milena Sokolowska https://orcid.org/0000-0001-9710-6685
Berber Vlieg-Boerstra https://orcid.org/0000-0001-7962-5406
Jens Walter https://orcid.org/0000-0003-1754-172X
Liam O'Mahony https://orcid.org/0000-0003-4705-3583

REFERENCES

1. Alkotob SS, Cannedy C, Harter K, et al. Advances and novel developments in environmental influences on the development of atopic diseases. *Allergy*. 2020;75:3077-3086.
2. Lunjani N, Satitsuksanoa P, Lukasik Z, Sokolowska M, Eiwegger T, O'Mahony L. Recent developments and highlights in mechanisms of allergic diseases: microbiome. *Allergy*. 2018;73(12):2314-2327.
3. Walter J, O'Mahony L. The importance of social networks-an ecological and evolutionary framework to explain the role of microbes in the aetiology of allergy and asthma. *Allergy*. 2019;74(11):2248-2251.
4. Martínez Leo EE, Segura Campos MR. Effect of ultra-processed diet on gut microbiota and thus its role in neurodegenerative diseases. *Nutrition*. 2020;71:110609.
5. Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. *Nature*. 2016;529(7585):212-215.
6. Stephen AM, Champ MMJ, Cloran SJ, et al. Dietary fiber in Europe: current state of knowledge on definitions, sources, recommendations, intakes and relationships to health. *Nutr Res Rev*. 2017;30(2):149-190.
7. Lunn JB, Buttriss JL. Carbohydrates and dietary fiber. *Nutr Bull* 2007;32(1):43, 21, 64.
8. EFSA Panel on Dietetic Products NaAN. Scientific opinion on the substantiation of health claims related to konjac mannan (glucomannan) and reduction of body weight (ID 854, 1556, 3725), reduction of post-prandial glycaemic responses (ID 1559), maintenance of normal blood glucose concentrations (ID 835, 3724), maintenance of normal (fasting) blood concentrations of triglycerides (ID 3217), maintenance of normal blood cholesterol concentrations (ID 3100, 3217), maintenance of normal bowel function (ID 834, 1557, 3901) and decreasing potentially pathogenic gastro-intestinal micro- organisms (ID 1558) pursuant to article 13(1) of regulation (EC) no 1924/2006. *EFSA J*. 2010;8:1798-1825. Available from: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2010.1798. Accessed November 2021
9. Bourquin LD, Titgemeyer EC, Fahey GC Jr. Vegetable fiber fermentation by human fecal bacteria: cell wall polysaccharide disappearance and short-chain fatty acid production during in vitro fermentation and water-holding capacity of unfermented residues. *J Nutr*. 1993;123(5):860-869.
10. Mcrorie JW, Fahey GC. A review of gastrointestinal physiology and the mechanisms underlying the health benefits of dietary fiber: matching an effective fiber with specific patient needs. *Clin Nurs Stud*. 2013;1:82-92.
11. Holscher HD. Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes*. 2017;8(2):172-184.
12. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J Nutr*. 1995;125(6):1401-1412.
13. Gibson GR, Hutkins R, Sanders ME, et al. Expert consensus document: the international scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol*. 2017;14(8):491-502.
14. Miqdady M, Al Mistarihi J, Azaz A, Rawat D. Prebiotics in the infant microbiome: the past, present, and future. *Pediatr Gastroenterol Hepatol Nutr*. 2020;23(1):1-14.
15. Cunningham M, Azcarate-Peril MA, Barnard A, et al. Shaping the future of probiotics and prebiotics. *Trends Microbiol*. 2021;29(8):667-685.
16. Zhu R, Fogelholm M, Poppitt SD, et al. Adherence to a plant-based diet and consumption of specific plant foods-associations with 3-year weight-loss maintenance and Cardiometabolic risk factors: a secondary analysis of the PREVIEW intervention study. *Nutrients*. 2021;13(11):3916.
17. Glenn AJ, Lo K, Jenkins DJA, et al. Relationship between a plant-based dietary portfolio and risk of cardiovascular disease: findings from the Women's Health Initiative prospective cohort study. *J Am Heart Assoc*. 2021;10(16):e021515.
18. McDonald D, Hyde E, Debelius JW, Morton JT, Gonzalez A, Ackermann G, et al. American gut: an open platform for citizen science microbiome research. *mSystems* 2018;3(3):e00031-18.
19. EFSA European Food Safety Authority. Scientific opinion on dietary reference values for carbohydrates and dietary fiber. EFSA panel on dietetic products, nutrition, and allergies. *EFSA J*. 2010;8(3):1462.
20. Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. *Nature*. 2012;486(7402):222-227.
21. Michalovich D, Rodriguez-Perez N, Smolinska S, et al. Obesity and disease severity magnify disturbed microbiome-immune interactions in asthma patients. *Nat Commun*. 2019;10(1):5711.
22. O'Keefe SJ, Li JV, Lahti L. Fat, fiber and cancer risk in African Americans and rural Africans. *Nat Commun*. 2015;28(6):6342.
23. Creedon AC, Hung ES, Berry SE, Whelan K. Nuts and their effect on gut microbiota, gut function and symptoms in adults: a systematic review and meta-analysis of randomised controlled trials. *Nutrients*. 2020;12:2347.
24. Lancaster SM, Lee-McMullen B, Abbott CW, et al. Global, distinctive, and personal changes in molecular and microbial profiles by specific fibers in humans. *Cell Host Microbe*. 2022;30:848-862.
25. Meslier V, Laiola M, Roager HM, et al. Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. *Gut*. 2020;69:1258-1268.
26. Ghosh TS, Rampelli S, Jeffery IB, et al. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. *Gut*. 2020;69:1218-1228.
27. Wang DD, Nguyen LH, Li Y, et al. The gut microbiome modulates the protective association between a Mediterranean diet and cardiometabolic disease risk. *Nat Med*. 2021;27:333-343.
28. El Kaoutari A, Armougom F, Gordon JI, Raoult D, Henrissat B. The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. *Nat Rev Microbiol*. 2013;11(7):497-504.
29. Rowland I, Gibson G, Heinken A, et al. Gut microbiota functions: metabolism of nutrients and other food components. *Eur J Nutr*. 2018;57(1):1-24.
30. Cantarel BL, Lombard V, Henrissat B. Complex carbohydrate utilization by the healthy human microbiome. *PLoS One*. 2012;7:e28742.
31. De Filippis F, Pasolli E, Tett A, et al. Distinct genetic and functional traits of human intestinal Prevotella copri strains are associated with different habitual diets. *Cell Host Microbe*. 2019;25:444-453.
32. Deehan EC, Yang C, Perez-Muñoz ME, et al. Precision microbiome modulation with discrete dietary fiber structures

directs short-chain fatty acid production. *Cell Host Microbe*. 2020;27(3):389-404.
33. Hamaker BR, Tuncil YE. A perspective on the complexity of dietary fiber structures and their potential effect on the gut microbiota. *J Mol Biol*. 2014;426:3838-3850.
34. Wastyk HC, Fragiadakis GK, Perelman D, et al. Gut-microbiota-targeted diets modulate human immune status. *Cell*. 2021;184:4137-4153.e14.
35. Cai Y, Folkerts J, Folkerts G, Maurer M, Braber S. Microbiota-dependent and -independent effects of dietary fiber on human health. *Br J Pharmacol*. 2020;177(6):1363-1381.
36. Majima A, Handa O, Naito Y, et al. Real-time monitoring of trans-epithelial electrical resistance in cultured intestinal epithelial cells: the barrier protection of water-soluble dietary fiber. *J Dig Dis*. 2017;18(3):151-159.
37. Kong C, Elderman M, Cheng L, De Haan BJ, Nauta A, De Vos P. Modulation of intestinal epithelial Glycocalyx development by human Milk oligosaccharides and non-digestible carbohydrates. *Mol Nutr Food Res*. 2019;63(17):e1900303.
38. Hino S, Sonoyama K, Bito H, Kawagishi H, Aoe S, Morita T. Low-methoxyl pectin stimulates small intestinal mucin secretion irrespective of goblet cell proliferation and is characterized by jejunum Muc2 upregulation in rats. *J Nutr*. 2013;143(1):34-40.
39. Akbari P, Braber S, Alizadeh A, et al. Galacto-oligosaccharides protect the intestinal barrier by maintaining the tight junction network and modulating the inflammatory responses after a challenge with the mycotoxin Deoxynivalenol in human Caco-2 cell monolayers and B6C3F1 mice. *J Nutr*. 2015;145(7):1604-1613.
40. Bhatia S, Prabhu PN, Benefiel AC, et al. Galacto-oligosaccharides may directly enhance intestinal barrier function through the modulation of goblet cells. *Mol Nutr Food Res*. 2015;59:566-573.
41. Brufau MT, Campo-Sabariz J, Bou R, et al. Salmosan, a β-galactomannan-rich product, protects epithelial barrier function in Caco-2 cells infected by salmonella enterica Serovar Enteritidis. *J Nutr*. 2016;146(8):1492-1498.
42. Ortega-González M, Ocón B, Romero-Calvo I, et al. Nondigestible oligosaccharides exert nonprebiotic effects on intestinal epithelial cells enhancing the immune response via activation of TLR4-NFκB. *Mol Nutr Food Res*. 2014;58(2):384-393.
43. Mendis M, Leclerc E, Simsek S. Arabinoxylan hydrolyzates as immunomodulators in lipopolysaccharide-induced RAW264.7 macrophages. *Food Funct*. 2016;7:3039-3045.
44. Mendis M, Leclerc E, Simsek S. Arabinoxylan hydrolyzates as immunomodulators in Caco-2 and HT-29 colon cancer cell lines. *Food Funct*. 2017;8:220-231.
45. Bermudez-Brito M, Sahasrabudhe NM, Rosch C, Schols HA, Faas MM, de Vos P. The impact of dietary fibers on dendritic cell responses in vitro is dependent on the differential effects of the fibers on intestinal epithelial cells. *Mol Nutr Food Res*. 2015;59:698-710.
46. Zenhom M, Hyder A, de Vrese M, Heller KJ, Roeder T, Schrezenmeir J. Prebiotic oligosaccharides reduce proinflammatory cytokines in intestinal Caco-2 cells via activation of PPARγ and peptidoglycan recognition protein 3. *J Nutr*. 2011;141:971-977.
47. Wismar R, Brix S, Frokiaer H, Laerke HN. Dietary fibers as immunoregulatory compounds in health and disease. *Ann N Y Acad Sci*. 2010;1190:70-85.
48. Bermudez-Brito M, Rosch C, Schols HA, Faas MM, de Vos P. Resistant starches differentially stimulate toll-like receptors and attenuate proinflammatory cytokines in dendritic cells by modulation of intestinal epithelial cells. *Mol Nutr Food Res*. 2015;59:1814-1826.
49. Lehmann S, Hiller J, van Bergenhenegouwen J, Knippels LM, Garssen J, Traidl-Hoffmann C. In vitro evidence for immune-modulatory properties of non-digestible oligosaccharides: direct effect on human monocyte derived dendritic cells. *PLoS One*. 2015;10:e0132304.
50. Sahasrabudhe NM, Beukema M, Tian L, et al. Dietary fiber pectin directly blocks toll-like receptor 2-1 and prevents doxorubicin-induced ileitis. *Front Immunol*. 2018;9:383.
51. Dang AT, Marsland BJ. Microbes, metabolites, and the gut-lung axis. *Mucosal Immunol*. 2019;12:843-850.
52. Duncan SH, Barcenilla A, Stewart CS, Pryde SE, Flint HJ. Acetate utilization and butyryl coenzyme a (CoA):acetate-CoA transferase in butyrate-producing bacteria from the human large intestine. *Appl Environ Microbiol*. 2002;68:5186-5190.
53. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell*. 2016;165:1332-1345.
54. Marinelli L, Martin-Gallausiaux C, Bourhis JM, Béguet-Crespel F, Blottière HM, Lapaque N. Identification of the novel role of butyrate as AhR ligand in human intestinal epithelial cells. *Sci Rep*. 2019;9:643.
55. Trompette A, Gollwitzer ES, Yadava K, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat Med*. 2014;20(2):159-166.
56. Antunes KH, Fachi JL, de Paula R, et al. Microbiota-derived acetate protects against respiratory syncytial virus infection through a GPR43-type 1 interferon response. *Nat Commun*. 2019;10(1):3273.
57. Zheng L, Kelly CJ, Battista KD, et al. Microbial-derived butyrate promotes epithelial barrier function through IL-10 receptor-dependent repression of Claudin-2. *J Immunol*. 2017;199:2976-2984.
58. Thio CL et al. Regulation of type 2 innate lymphoid cell-dependent airway hyperreactivity by butyrate. *J Allergy Clin Immunol*. 2018;142:1867-1883.
59. Folkerts J, Redegeld F, Folkerts G, et al. Butyrate inhibits human mast cell activation via epigenetic regulation of FcεRI-mediated signaling. *Allergy*. 2020;75:1966-1978.
60. O'Mahony L. Short chain fatty acids modulate mast cell activation. *Allergy*. 2020;75:1848-1849.
61. Sepahi A, Liu Q, Friesen L, Kim CH. Dietary fiber metabolites regulate innate lymphoid cell responses. *Mucosal Immunol*. 2021;14:317-330.
62. Macia L, Tan J, Vieira AT, et al. Metabolite-sensing receptors GPR43 and GPR109A facilitate dietary fibre-induced gut homeostasis through regulation of the inflammasome. *Nat Commun*. 2015;6:6734.
63. Daïen CI, Tan J, Audo R, et al. Gut-derived acetate promotes B10 cells with antiinflammatory effects. *JCI Insight*. 2021;6:e144156.
64. Roduit C, Frei R, Ferstl R, et al. High levels of butyrate and propionate in early life are associated with protection against atopy. *Allergy*. 2019;74(4):799-809.
65. Tan J, McKenzie C, Vuillermin PJ, et al. Dietary fiber and bacterial SCFA enhance Oral tolerance and protect against food allergy through diverse cellular pathways. *Cell Rep*. 2016;15(12):2809-2824.
66. Paparo L, Nocerino R, Ciaglia E, Di Scala C, et al. Butyrate as bioactive human milk protective component against food allergy. *Allergy*. 2020;76(5):1398-1415.
67. Arpaia N, Campbell C, Fan X, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature*. 2013;504(7480):451-455.
68. Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature*. 2013;504(7480):446-450.
69. Venter C, Palumbo MP, Glueck DH, et al. The maternal diet index in pregnancy is associated with offspring allergic diseases: the healthy start study. *Allergy*. 2022;77:162-172.
70. Merino J, Joshi AD, Nguyen LH, et al. Diet quality and risk and severity of COVID-19: a prospective cohort study. *Gut*. 2021;70:2096-2104.
71. Jagielski P, Łuszczki E, Wnęk D, et al. Associations of nutritional behavior and gut microbiota with the risk of COVID-19 in healthy young adults in Poland. *Nutrients*. 2022;14(2):350.

72. Kim H, Rebholz CM, Hegde S, et al. Plant-based diets, pescatarian diets and COVID-19 severity: a population-based case-control study in six countries. *BMJ Nutr Prev Health*. 2021;4:257-266.
73. Albrich WC, Ghosh TS, Ahearn-Ford S, et al. A high-risk gut microbiota configuration associates with fatal hyperinflammatory immune and metabolic responses to SARS-CoV-2. *Gut Microbes*. 2022;14:2073131.
74. Lunjani N, Albrich WC, Suh N, et al. Higher levels of bacterial DNA in serum associate with severe and fatal COVID-19. *Allergy*. 2022;77:1312-1314.
75. Orel R, Rebersak LV. Clinical effects of prebiotics in pediatric population. *Indian Pediatr*. 2016;53(12):1083-1089.
76. Cuello-Garcia CA, Fiocchi A, Pawankar R, et al. World allergy organization-McMaster University guidelines for allergic disease prevention (GLAD-P): prebiotics. *World Allergy Organ J*. 2016;9:10.
77. Cuello-Garcia C, Fiocchi A, Pawankar R, et al. Prebiotics for the prevention of allergies: a systematic review and meta-analysis of randomized controlled trials. *Clin Exp Allergy*. 2017;47(11):1468-1477.
78. Recto MST, Genuino MLG, Castor MAR, et al. Dietary primary prevention of allergic diseases in children: the Philippine guidelines. *Asia Pac Allergy*. 2017;7(2):102-114.
79. Garcia-Larsen V, Lerodiakonou D, Jarrold K, et al. Diet during pregnancy and infancy and risk of allergic or autoimmune disease: a systematic review and meta-analysis. *PLoS Med*. 2018;15(2):e1002507.
80. Skorka A, Piescik-Lech M, Kolodziej M, Szajewska H. Infant formulae supplemented with prebiotics: are they better than unsupplemented formulae? An updated systematic review. *Br J Nutr*. 2018;119(7):810-825.
81. Sierra C, Bernal MJ, Blasco J, et al. Prebiotic effect during the first year of life in healthy infants fed formula containing GOS as the only prebiotic: a multicentre, randomised, double-blind and placebo-controlled trial. *Eur J Nutr*. 2015;54:89-99.
82. Ivakhnenko OS, Nyankovskyy SL. Effect of the specific infant formula mixture of oligosaccharides on local immunity and development of allergic and infectious disease in young children: randomized study. *Pediatr Pol*. 2013;88:398-404.
83. de Silva D, Halken S, Singh C, et al. Preventing food allergy in infancy and childhood: systematic review of randomised controlled trials. *Pediatr Allergy Immunol*. 2020;31(7):813-826.
84. Andrianasolo RM, Hercberg S, Kesse-Guyot E, et al. Association between dietary fiber intake and asthma (symptoms and control): results from the French national e-cohort NutriNet-Santé. *Br J Nutr*. 2019;122:1040-1051.
85. Bseikri M, McCann JC, Lal A, et al. A novel nutritional intervention improves lung function in overweight/obese adolescents with poorly controlled asthma: the supplemental nutrition in asthma control (SNAC) pilot study. *FASEB J*. 2018;32:6643-6654.
86. McLoughlin R, Berthon BS, Rogers GB, et al. Soluble fiber supplementation with and without a probiotic in adults with asthma: a 7-day randomised, double blind, three way cross-over trial. *EBioMedicine*. 2019;46:473-485.
87. Saeed MA, Gribben KC, Alam M, Lyden ER, Hanson CK, LeVan TD. Association of Dietary Fiber on asthma, respiratory symptoms, and inflammation in the adult National Health and nutrition examination survey population. *Ann Am Thorac Soc*. 2020;17(9):1062-1068.
88. Grieger JA, Grzeskowiak LE, Wood LG, Clifton VL. Asthma control in pregnancy is associated with pre-conception dietary patterns. *Public Health Nutr*. 2016;19(2):332-338.
89. Pretorius RA, Bodinier M, Prescott SL, Palmer DJ. Maternal fiber dietary intakes during pregnancy and infant allergic disease. *Nutrients*. 2019;11(8):1767.
90. Williams NC, Johnson MA, Shaw DE, et al. A prebiotic galactooligosaccharide mixture reduces severity of hyperpnoea-induced bronchoconstriction and markers of airway inflammation. *Br J Nutr*. 2016;116(2):798-804.
91. Derakhshan A, Khodadoost M, Ghanei M, et al. Effects of a novel barley-based formulation on allergic rhinitis: a randomized controlled trial. *Endocr Metab Immune Disord Drug Targets*. 2019;19(8):1224-1231.
92. Ido Y, Nagamine T. The effect of prebiotic lactosucrose on serum IgE levels in allergic people: a pilot study in Japan. *Intern Med J*. 2018;25:389-390.
93. Matano Y, Morita T, Ito M, et al. Dietary habits in Japanese patients with chronic spontaneous urticaria. *Australas J Dermatol*. 2020;61(3):e333-e338.
94. Bozensky J, Hill M, Zelenka R, Skyba T. Prebiotics do not influence the severity of atopic dermatitis in infants: a randomised controlled trial. *PLoS One*. 2015;10(11):e0142897.
95. Boyle RJ, Tang MLK, Chiang WC, et al. Prebiotic-supplemented partially hydrolysed cow's milk formula for the prevention of eczema in high-risk infants: a randomized controlled trial. *Allergy*. 2016;71(5):701-710.
96. Wopereis H, Sim K, Shaw A, Warner JO, Knol J, Kroll JS. Intestinal microbiota in infants at high risk for allergy: effects of prebiotics and role in eczema development. *J Allergy Clin Immunol*. 2018;141:1334-1342.
97. Ranucci G, Buccigrossi V, Borgia E, et al. Galacto-oligosaccharide/Polidextrose enriched formula protects against respiratory infections in infants at high risk of atopy: a randomized clinical trial. *Nutrients*. 2018;10(3):286.
98. Koga Y, Tokunaga S, Nagano J, et al. Age-associated effect of kestose on *Faecalibacterium prausnitzii* and symptoms in the atopic dermatitis infants. *Pediatr Res*. 2016;80(6):844-851.
99. Grüber C, van Stuivenberg M, Mosca F, et al. Immunoactive prebiotics transiently prevent occurrence of early atopic dermatitis among low-atopy-risk infants. *J Allergy Clin Immunol*. 2015;136(6):1696-1698.
100. Pontes MV, Ribeiro TCM, Ribeiro H, et al. Cow's milk-based beverage consumption in 1- to 4-year-olds and allergic manifestations: an RCT. *Nutr J*. 2016;15:19.
101. Venter C, Greenhawt M, Meyer RW, et al. EAACI position paper on diet diversity in pregnancy, infancy and childhood: novel concepts and implications for studies in allergy and asthma. *Allergy*. 2020;75(3):497-523.
102. Armet AM, Deehan EC, O'Sullivan AF, et al. Rethinking healthy eating in light of the gut microbiome. *Cell Host Microbe*. 2022;30:764-785.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Venter C, Meyer RW, Greenhawt M, et al. Role of dietary fiber in promoting immune health—An EAACI position paper. *Allergy*. 2022;77:3185-3198. doi: 10.1111/all.15430