Potential Biomarkers, Risk Factors, and Their Associations with IgE-Mediated Food Allergy in Early Life: A Narrative Review

Caroline E Childs,1,2 Daniel Munblit,3,4 Laurien Ulfman,6 Carlos Gómez-Gallego,7 Liisa Lehtoranta,8 Tobias Recker,9 Seppo Salminen,10 Machtedl Tiemessen,11 and Maria Carmen Collado12

1School of Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, United Kingdom; 2Institute for Life Sciences, University of Southampton, Southampton, United Kingdom; 3Imperial College London, London, United Kingdom; 4Department of Paediatrics and Paediatric Infectious Diseases, Institute of Child’s Health, Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia; 5Inflammation, Repair and Development Section, National Heart and Lung Institute, Faculty of Medicine, Imperial College London, London, United Kingdom; 6FrieslandCampina, Amersfoort, The Netherlands; 7Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland; 8IFF Health, International Flavours & Fragrances, Finland; 9ILSI Europe, Belgium; 10University of Turku, Finland; 11Danone Nutricia Research, The Netherlands; and 12Institute of Agrochemistry and Food Technology-National Research Council (IATA-CSIC), Valencia, Spain

ABSTRACT

Food allergy (FA) affects the quality of life of millions of people worldwide and presents a significant psychological and financial burden for both national and international public health. In the past few decades, the prevalence of allergic disease has been on the rise worldwide. Identified risk factors for FA include family history, mode of delivery, variations in infant feeding practices, prior diagnosis of other atopic diseases such as eczema, and social economic status. Identifying reliable biomarkers that predict the risk of developing FA in early life would be valuable in both preventing morbidity and mortality and by making current interventions available at the earliest opportunity. There is also the potential to identify new therapeutic targets. This narrative review provides details on the genetic, epigenetic, dietary, and microbiome influences upon the development of FA and synthesizes the currently available data indicating potential biomarkers. Whereas there is a large body of research evidence available within each field of potential risk factors, there is a very limited number of studies that span multiple methodological fields, for example, including immunology, microbiome, genetic/epigenetic factors, and dietary assessment. We recommend that further collaborative research with detailed cohort phenotyping is required to identify biomarkers, and whether these vary between at-risk populations and the wider population. The low incidence of oral food challenge–confirmed FA in the general population, and the complexities of designing nutritional intervention studies will provide challenges for researchers to address in generating high-quality, reliable, and reproducible research findings. Adv Nutr 2021;00:1–19.

Statement of Significance: Food allergy affects the quality of life of millions of people worldwide and presents a significant psychological and financial burden for both national and international public health. Identifying reliable biomarkers that predict the risk of developing food allergy would be valuable in both preventing morbidity and mortality and by making current interventions available at the earliest opportunity. This review provides details on the genetic, epigenetic, dietary, and microbiome influences upon the development of food allergy. This helps in identifying reliable biomarkers to predict the risk of developing food allergy, which could be valuable in both preventing morbidity and mortality and by making interventions available at the earliest opportunity.

Keywords: IgE-mediated food allergy, biomarkers, pathways, risk factors, microbiota, nutrition, infant diet

Introduction

Food allergy (FA) is defined as an adverse immunological response to a food protein (1). It affects the quality of life of millions worldwide and presents a significant psychological (2) and financial (3) burden for both national and international public health. The European Academy of Allergy and Clinical Immunology (EAACI) systematic review estimates FA prevalence in Europe at between 0.1% and 6.0% (4). Risk factors for developing FA are multiple and contextual, ranging from genetic predisposition to environmental factors (such as mode of birth delivery, type and timing of solid food introduction, changes in hygiene

© The Author(s) 2021. Published by Oxford University Press on behalf of the American Society for Nutrition. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com. Adv Nutr 2021;00:1–19; doi:https://doi.org/10.1093/advances/nmab122.
practices, and socioeconomic status) and the interaction between these factors (Table 1).

Identifying biomarkers that reflect either the risk of developing FA, the severity of FA, or induction of tolerance (i.e., reaching nonreactivity toward a substance that would previously cause a reaction) would be valuable in both preventing morbidity and mortality arising from FA, by allowing earlier interventions and by potentially highlighting new targets for intervention. The Health Biomarkers Definitions Working Group defined a biomarker as “a characteristic that is objectively measured and evaluated as an indicator..." of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (5).

Biomarkers can also provide value in the regulatory context. The European Food Safety Authority health claim substantiation requires that “a food or one of its constituents significantly reduces a risk factor in the development of a human disease” (6). The regulation additionally requires that the risk factor is “generally accepted.” A classic example is cholesterol, a biomarker found to be associated with heart disease development. In labeling or advertising, health claims that constitute a “reduction of disease risk” shall also bear a statement indicating that the disease to which the claim is referring has multiple risk factors and that altering one of these risk factors might or might not have a beneficial effect. Thus, the optimal risk biomarker to be altered would be a combination of risk factors or a chain of events reflecting changes in the RR.

This article reviews available evidence in human studies in early life about well-described pathways with well-defined biomarkers and risk factors that are associated with IgE-mediated FA.

### Current Status of Knowledge

Recent efforts have focused on the identification of biomarkers for prediction and diagnosis of IgE-mediated FA. IgE-mediated reactions induce a variety of symptoms that range from erythema, urticaria and angioedema, nausea, abdominal pain or vomiting, to severe respiratory distress, or cardiovascular collapse among others (7). Differences in the outcomes and manifestations might be related to genetic components but also to environmental factors, dietary factors, and the intestinal microbiota (8). The exact

| Factors increasing microbial dysbiosis | Factors improving microbial equilibrium | Factors with no proven impact on microbial dysbiosis/equilibrium |
|----------------------------------------|----------------------------------------|---------------------------------------------------------------|
| Antibiotic use during pregnancy        | Early cutaneous exposure to food allergens in the environment | Early oral exposure to foods                                  |
| and first year of life                 | Family history of allergic disease      |                                                               |
| Cesarean delivery                      | Prior diagnosis of atopic disease        |                                                               |
| Exposure to bacterial enterotoxins     | like eczema                              |                                                               |
| Vitamin D deficiency                   | Higher socioeconomic status              |                                                               |
|                                       | Living in developed societies           |                                                               |

**Table 1** Summary of the most common and specific determinants impacting microbiota and risk of developing food allergy
diagnosis and prevalence of FA is difficult to ascertain due to the imprecision of laboratory tests and the lack of specific biomarkers, relying on the combination of the clinical history of characteristic symptoms together with test results (7), the use of IgE as a biomarker in FA, and the potential associations with genetic and epigenetic origins that would be targets of potential interventions (breast milk compared with others, weaning, diet, etc.).

**Genetic and epigenetic biomarkers of FA**

The link between the risk of FA in children and allergic diseases and/or allergic sensitization in their family has been extensively reported (9–14), with estimates that FA/sensitization risk doubles if 1 parent has an allergic disease, and is 3-fold higher if both parents have an allergic disease. A meta-analysis of genome-wide association studies identified 10 loci in or near TLR6 (toll like receptor 6), C11orf30 (EMSY transcriptional repressor, BRCA2 interacting), STAT6 (signal transducer and activator of transcription 6), SLC25A46 (solute carrier family 25 member 46), HLA-DQB1 (human leukocyte antigen DQ isotype B1), IL1RL1 (interleukin 1 receptor like 1), LPP (LIM domain containing preferred translocation partner in lipoma), MYC (MYC proto-oncogene, bHLH transcription factor), IL2 (interleukin 2), and HLA-B (major histocompatibility complex, class I, B), that are associated with allergic sensitization (15). Allergen-specific genetic modifications in the HLA DR and DQ isotype gene region have also been associated with peanut allergy (16). Conflicting results were reported with regard to gender association with FA and no conclusive studies are available (10, 11, 17, 18). Some data suggest that 5 loci at genome-wide significance (clade B serpin, or SERPINB) gene cluster at 18q21.3, the cytokine gene cluster at 5q31.1, the filaggrin gene, the C11orf30/LRRC32 (leucine rich repeat containing 32) locus, and the HLA region increase the risk of FA (19).

Eczema and FA often coexist, and evidence suggests that an impaired skin barrier is a significant risk factor for FA development later in life (20, 21) with loss-of-function variants in the filaggrin gene suggested as a causative factor; moreover, filaggrin mutation is associated with eczema and asthma later in life (22, 23). Identified genetic loci associated with FA, their potential mode of action, and evidence supporting their use as biomarkers are presented in Table 2.

Extrinsic environmental factors including diet, pollutants, and infections, and intrinsic factors such as the intestinal microbiota and inflammatory state are likely to play a crucial role in inducing epigenetic changes (24, 25). Postnatal factors and environmental influence are risk factors for FA development and this exposure accumulates while the infant develops (9, 10, 18). The route of exposure (e.g., placental, skin, breast milk, airway, gut), timing, dose of allergen exposure, and host immune system status are likely to impact upon the potential for epigenetic change (26). Investigations of targeted and untargeted methylation profiles of immune cells are methodologies that can help to find biomarkers that reflect the different stages of FA: those at risk, those who are tolerant, and those with active disease (27, 28). An overview of studies on epigenetic changes associated with FA is presented in Table 3.

**The role of breastfeeding, and time of food introduction in FA**

**Breastfeeding.**

Human milk is the first food available to a newborn baby, and exclusive breastfeeding for the duration of 6 mo is recommended by the WHO. Available evidence suggests that breastfeeding protects against infections as well as offering long-term benefits, reducing the risk of hypertension and diabetes, and improving cognitive development (29). The protective effect of breast milk on allergy development has not been fully demonstrated (29–33). However, there are conflicting data concerning the relation between breastfeeding and FA, with some cohort studies reporting a reduced risk of FA development in the general population (20, 21) and in high-risk children (34) and others reporting an increased risk (35, 36). One meta-analysis investigating this relation reported no evidence of breastfeeding’s protective effect in preventing FA development (OR: 1.02; 95% CI: 0.88, 1.18), although the authors suggested that the risk of bias and major differences in the outcome definitions in the current studies might be responsible for the inconclusive results (31). Because human milk contains food proteins, their concentrations in the milk and maternal diet might also contribute to tolerance development (37), particularly in the presence of the biologically active molecules (38). Both aspects are not normally considered in the studies assessing associations between breastfeeding and noncommunicable diseases development.

A recent systematic review on FA prevention suggests that although breastfeeding has many benefits for infants and mothers, it might not reduce the risk of FA (39). Human breast milk constituents vary (over time postpartum, within and between women, and even within the same feed), which could, in part, explain some of the conflicting results of general observational studies regarding the provision of breastfeeding (40, 41). It has been described that immunological compounds in breast milk (including cytokines and IgGs) are modulated by multiple factors, including maternal allergic status, parity, and geographical location among others (42–45), but overall evidence on the topic is conflicting with most of the studies not identifying clear associations between the immunological composition of breast milk and allergic disease development in infants (38). Dietary peptides from proteins in food are excreted in breast milk, but these have relatively short sequences and are in small amounts; therefore, their sensitization or tolerogenic potential remains to be explored (46). The presence of specific peptides has also been shown in infant formula (47). However, so far, systematic reviews (48, 49) have not found sufficient evidence that hydrolyzed formula prevents eczema or milk allergy (50).
TABLE 2 Genetic loci associated with food allergy, their potential link with food allergy, and evidence supporting their use as biomarkers

| Name | Genetic risk factor | Role | Potential link with FA | Reported utility as biomarker? | References |
|------|---------------------|------|------------------------|--------------------------------|------------|
| Toll-like receptor 6 | TLR6 | Pathogen recognition and activation of innate immunity | TLR function can be altered by early environmental and microbial exposures | Generally associated with allergic sensitization | (15, 145) |
| EMSY transcriptional repressor | C1orf30 | Repressor of BRCA2 protein | Involved in epigenetic regulation of gene expression | Identified as genetic risk factor for peanut allergy and food allergy | (15, 146) |
| Signal transducer and activator of transcription 6 | STAT6 | Central role in IL4-mediated responses | Polymorphisms have been associated with age of tolerance induction | Age of tolerance development for cow milk was significantly higher in children with the GG genotype at rs324015 of the STAT6 gene compared with those with the AA + AG genotype [2y (range = 1.5–3.9y) vs. 1.2y (range = 1.0–2.2y); P = 0.02] | (15, 147) |
| Solute carrier family 25 member 46 | SLC25A46 | Promotes mitochondrial fission and prevents the formation of hyperfilamentous mitochondria | Involved in the association between food allergy and atopic dermatitis | Polymorphism SLC25A46 was associated with higher risk of food allergy | (15, 148) |
| Major histocompatibility complex, class II, DQ beta 1 | HLA-DQB1 | Plays a central role in the immune system by presenting peptides derived from extracellular proteins | Peanut allergic-specific loci in the human leukocyte antigen (HLA)-DQ and -DR regions were found in a large cohort study | Several polymorphisms associated with peanut, milk, and egg allergy | (15, 16, 149) |
| Interleukin 1 receptor-like 1 | IL1RL1 | Involved in the function of helper T cells | ST2, β-chain of IL33 receptor | Generally associated with allergic sensitization | (15) |
| LIM domain containing preferred translocation partner in lipoma | LPP | Involved in cell-cell adhesion and cell motility. This protein also shuttles through the nucleus and may function as a transcriptional coactivator | Allergic sensitization | Generally associated with allergic sensitization | (15) |
| MYC proto-oncogene, bHLH transcription factor | MYC | Plays a role in cell cycle progression, apoptosis, and cellular transformation | Downregulated in children with food allergy | Generally associated with allergic sensitization and food allergy | (15, 150) |
| Interleukin 2 | IL2 | Proliferation of T and B lymphocytes | Allergic sensitization | Generally associated with allergic sensitization | (15) |
| Major histocompatibility complex, class I B | HLA-B | Central role in the immune system by presenting peptides derived from the endoplasmic reticulum lumen | Allergic sensitization | Generally associated with allergic sensitization | (15) |

(Continued)
| Name                  | Genetic risk factor | Role                                           | Potential link with FA                                                                 | Reported utility as biomarker?                                                                                   | References |
|-----------------------|---------------------|------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|------------|
| Filaggrin             | FLG                 | Role in skin barrier function                  | Indirect association with food allergy                                                    | Filaggrin loss-of-function mutations are associated with food allergy in older children via eczema and food allergen sensitization in their early childhood | (20, 21, 23, 151) |
| Interleukin 13        | IL13                | Involved in several stages of B-cell maturation and differentiation | IL13 polymorphism rs1295686 (in complete linkage disequilibrium with functional variant rs20541) is associated with challenge-proven food allergy | IL13 gene polymorphisms have also been identified as biomarkers of IgE-mediated food allergy and are a predictor of cord blood IgE concentrations | (152)     |
| Catenin alpha 3       | CTNNA3              | Cell-cell adhesion                              | Knockdown of CTNNA3 resulted in upregulation of CD63 and CD203c in mononuclear cells upon PMA stimulation | Copy number variation impacting CTNNA3 has been associated with pediatric food allergy                            | (153)     |
| RNA binding fox-1 homolog 1 | RBFOX1               | Regulates alternative splicing events          | Association with food allergy at a genome-wide scale                                      | Generally associated with pediatric food allergy                                                                | (153)     |
| GC vitamin D binding protein | GC/DBP               | Binds to vitamin D and its plasma metabolites and transports them to target tissues | Gg genotype produces less vitamin D binding protein (DBP)                                  | Vitamin D deficiency linked with Gg genotype producing less vitamin D binding protein (DBP) was associated with a higher prevalence of egg and peanut allergy in 1- and 2-year-old infants | (154)     |
| Indoleamine 23-dioxygenase 1 | IDO1                | Modulates T-cell behavior                      | High IDO activity is associated with nonresponsiveness to food allergens despite allergen sensitization | Associated with tolerance to food allergens                                                                     | (155)     |
| Sirtuin 1             | SIRT1               | Functions of human sirtuins have not yet been determined | Negatively regulates FcεRI-stimulated mast cell activation and anaphylaxis                  | Generally associated with anti-inflammatory response                                                            | (156, 157) |

1 BRCA2, Breast Cancer Type 2 susceptibility protein; FcεRI, high-affinity IgE receptor; PMA, phorbol myristate acetate.
| Study | Where identified | Main findings | Potential mechanism of action | Reported utility as biomarker? | References |
|-------|-----------------|---------------|-------------------------------|-------------------------------|------------|
| DNA methylation profiles (~450,000 CpGs) of peripheral immune cells (CD4+ T cells) | Children with IgE-mediated food allergy | 179 differentially methylated sites of loci associated with the disease phenotype, and 96 CpG sites DNA methylation profile discriminated food-allergic vs. healthy infants | MAP kinase pathway → dysregulation of DNA methylation at MAPK signaling–associated genes during early CD4+ T-cell development may contribute to suboptimal T-lymphocyte responses in early childhood associated with the development of food allergy | Predicted clinical outcomes with an accuracy of almost 80% MAP kinase pathway was most prominently associated with CpGs that were predictive of food challenge | (158, 159) |
| DNA methylation profiles | Egg allergy | DNA methylation profiles of T cells discriminate infants with persistent egg allergy compared with those who had outgrown egg allergy | Methylation of metabolic (RPTOR, PI3CD, MAPK, FOXO1) and inflammatory genes (IL1R, IL11R, MAPK, IL6) affected | Data about predictive potential not available | (150) |
| DNA methylation profiles | Cow milk allergy | Cow milk allergic infants showed hypermethylation in whole blood compared with controls and tolerant group | Differential methylation patterns on DHX58 (innate immune response), ZNF281 (transcriptional regulation), EIF42A (interferon pathway), and HTR2 (smooth muscle contraction) between groups | Data about predictive potential not available | (160) |
| DNA methylation profiles and single-nucleotide polymorphisms | Peanut allergy | DNA methylation of the HLA-DOA1 and HLA-DRB1, IL4, IL12Rb1, IL2, BDNF, IL17, CXCL12, CCR7, runt-related transcription factor 1 (RUNX1), CD3e, and SERPINE1 IL1B and IL6 has been associated with peanut allergy | Increased protein secretion in response to allergen-specific stimulation | DNA methylation signature combinations may have superior diagnostic potential than serum peanut–specific IgE | (16) |
| Th1-Th2 | Cow milk allergy | DNA methylation profiles differ with cow milk allergy | DNA methylation profiles of IL4, IL5, IL10, and IFNγ genes between infants with active cow milk allergy and those who outgrew their cow milk allergy | GATA3 in Th2 cells Ex vivo PBMC cytokine profile in predicting cow milk allergy: TNF, IL10, IL12 higher in cow milk allergy patients compared with controls | (161–163) |
| Study | Where identified | Main findings | Potential mechanism of action | Reported utility as biomarker? | References |
|-------|------------------|---------------|------------------------------|--------------------------------|------------|
| Th1-Th2 | Cow milk allergy | DNA methylation of FOXP3, Th1/Th2 cytokine genes in IgE-mediated allergy, in children with cow milk allergy treated with an extensively hydrolyzed formula including a probiotic (test formula) vs. a control formula | FOXP3, IL10, and IFNγ demethylation rate was higher, and IL4 and IL5 demethylation rate was lower in the test formula group | Intervention promotes regulatory and immune suppressive immune factors and at the same time decreases activity of Th2 type genes | (164) |
| FOXP3 | Peanut-allergic infants and cow milk-allergic infants | Immune-tolerant participants had ↑ai-T reg with greater suppressive function, and with ↑FOX3 hypomethylation | Oral immunotherapy in peanut allergic infants increased antigen-induced regulatory T-cell function and hypomethylation of FOXP3 in infants that became tolerant | Data about predictive potential not available | (165) |
| | Cow milk allergy | ↓FOX3 gene demethylation in children with active IgE-mediated cow milk allergy | Formula selection influenced the FOXP3 T-cell-specific demethylation region demethylation profile | Data about predictive potential not available | (166) |
| | Methylated levels taken from mononuclear blood cells at 405,658 CpG islands across the genome (machine learning approach) | 40 samples for training, 10 samples for cross-validation, and 8 completely hidden samples for testing | Novel 13-gene signature to diagnose clinical reactivity: chr1p13 (SARS), chr7p22 (MAPK), chr11q14 (PAW3), chr9p22 (SLC2A2), chr8p21 (KIF13B), chr10q22 (CTBP2), chr10q11 (ARID5B), and chr10q23 (FAM190B) | The 18-CpG signature mapped to several canonical Wnt pathways, G0, and positional gene sets with functional association with the immune system | (167) |

1ai, antigen-induced; ARID5B, AT-rich interaction domain 5B; BDNF, brain-derived neurotrophic factor; CCR7, C-C motif chemokine receptor 7; chr, chromosome; CTBP2, C-terminal binding protein 2; CXCL12, C-X-C motif chemokine ligand 12; DHX58, DExH-box helicase 58; EIF4A2, eukaryotic translation initiation factor 4A2; FA, food allergy; FOX01, forkhead Box O1; FOX3, forkhead box P3; GATA3, GATA binding protein 3; GO, The Generic Gene Ontology; HLA, human leukocyte antigen; HTRA2, HtrA serine peptidase 2; KIF13B, kinesin family member 13B; MAPK, MAPK transcription factor K; MAPK1, mitogen-activated protein kinase 1; PANX1, pannexin 1; PBMCs, peripheral blood mononuclear cells; PIK3CD, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta; RPTOR, regulatory associated protein of mTOR complex 1; SARS, seryl-tRNA synthetase; SLC2A2, solute carrier family 24 member 2; Th, helper T cells; Treg, regulatory T cells; ZNF281, Zinc Finger Protein 281.
Thus, claims currently appearing on infant formula products need better substantiation and many reputable organizations, including the American Academy of Pediatrics; American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and Canadian Society for Allergy and Clinical Immunology, concluded that “there is no protective benefit from the use of hydrolyzed formula in the first year of life against food allergy or food sensitization” (51, 52). A recent study suggested that avoiding temporary supplementation with conventional cow milk formula in the first 3 d of life can result in a large decrease in the risk of FA in early childhood (53), but this requires further confirmation.

Weaning and food introduction.
Delaying the introduction of solid food until 6 mo remains the current WHO recommendation. Yet recent expert opinion has investigated the hypothesis that oral tolerance can be induced by modifying the timing and diversity of early food exposure (54). Supportive data for this hypothesis are coming predominantly from 2 large high-quality randomized controlled trials (RCTs), The Learning Early about Peanut Allergy (LEAP) and Enquiring About Tolerance (EAT). The LEAP study demonstrated a significant reduction in peanut allergy prevalence in children at high risk of allergy development, who were consuming peanuts between 4 and 11 mo old on a regular basis (55). There was an earlier and greater increase in peanut-specific IgG and IgG4 in the early consumption group compared with the avoidance group. In both groups the mean peanut-specific IgE concentrations were highly comparable and increased over time, albeit there were more participants in the avoidance group with very high IgE concentrations (55). The EAT trial looked at early food introduction (from 3 mo old) and concluded that it might decrease the risk of FA development (56). The authors reported significantly lower RR of peanut and egg allergy in the early introduction group, with no difference in the prevalence of milk, sesame, fish, or wheat allergy. Risk reduction was shown in per protocol analysis only, whereas no statistically significant difference was found in intention-to-treat analysis. Studies reporting contradictory results to EAT exist (57), but they are often considered of lower robustness.

With an apparent shift in expert opinion toward early introduction of certain highly allergenic foods, the American National Institute of Allergy and Infectious Diseases updated its guidelines on peanut allergy prevention in 2017 (58), recommending that peanut-containing food introduction should occur between 4 and 6 mo of age in egg-allergic infants and/or babies with severe eczema, and at 6 mo of age for infants with mild-to-moderate eczema. Recent guidelines from the American Academy of Pediatrics support these recommendations (52).

In their systematic review on FA prevention, the authors concluded that available evidence suggests that “introduction of small amounts of cooked egg into the infant diet as part of complementary feeding probably reduces the risk of egg allergy in infancy and in countries with a high prevalence of peanut allergy, introducing regular peanut consumption from 4–11 months of life in infants at increased risk probably results in a large reduction in peanut allergy in early childhood compared to completely avoiding peanut for the first five years” (39). In contrast, no reduction in FA incidence was found when multiple potential food allergens were simultaneously introduced into the infant diet from age 3 mo (56). Diet diversity during the first year of life might also have a positive role in determining the risk of FA. An increased diversity of complementary foods introduced in the first 12 mo of life was inversely associated with FA development up to 6 y old (59).

Is there a need for biomarkers to monitor dietary interventions to induce tolerance?
Food avoidance remains the main therapeutic approach in FA management, but researchers and clinicians are continuously seeking for intervention options. Controlled exposure to the allergens was suggested as a potential option for tolerance induction. Indeed, in recent years, oral immunotherapy (OIT) has been applied for several allergens to investigate whether desensitization and/or sustained unresponsiveness development is possible. A meta-analysis on the effect of OIT in reducing prevalence of cow milk allergy (CMA) concluded it is an effective therapy (60); however, frequency of adverse events is high and validity of outcome selection used to measure the efficacy of OIT is still unclear. Looking at an individual study level, there was no association of OIT in children (aged 6–17 y) and IgE concentrations between the treated and the control group, whereas IgG4 was significantly increased in the posttreatment group after OIT but there was only a slight increase in the control group (61). Recently, a cohort of 137 peanut-allergic child and adult patients (aged 6–26 y) were compared with non–peanut-allergic controls and differences between IgE, IgG4, and the ratio of IgG4/IgE were examined (62).

These observations would imply that more data are needed on specific immunoglobulin E (sIgE) and IgG4 in monitoring tolerance induction over time before it can be concluded that these are reliable biomarkers for tolerance induction. There could be more potential for the increase in IgG4 in oral tolerance induction than the decrease in IgE. It is very important to note that there are no agreed core outcome measures in FA trials, which do not allow for appropriate effectiveness/efficacy evaluation (63). Different immunological parameters are currently used as end points in OIT trials, but available evidence of their importance is very limited (64).

What Is the Role of the Microbiota in FA?
A link between IgE-mediated FA and the gut microbiota composition and metabolic activity has been suggested. A recent study including 233 infants (>4 y old) with FA (milk, sesame, peanut, and tree nuts), and nonallergic controls showed a distinct microbial profile for FA to different foods.
characterized with an underrepresentation of *Prevotella copri* (65). In agreement, maternal carriage of *Prevotella copri* during pregnancy was also linked to a decreased risk of FA during infancy (66). Growing evidence supports a role for the gut microbiome in the pathogenesis and course of FA, with microbial dysbiosis preceding the development of FA (67). It has been reported that an elevated *Enterobacteriaceae/Bacteroidaceae* ratio in early infancy as well as lower microbial species richness in the infant (*n* = 166, ages 3 and 12 mo) might be a predictor of egg, milk, and peanut sensitization (determined by skin prick test) at age 12 mo, adjusting for birth delivery mode, antibiotic use, or breastfeeding (68). This raises the question of whether FA can be predicted using gut microbiome biomarkers (69). A study with 319 subjects enrolled in the Canadian Healthy Infant Longitudinal Development (CHILD) study showed that infants at risk of asthma exhibited transient gut microbial dysbiosis during the first 100 d of life characterized by lower relative abundance of *Lachnospira*, *Veillonella*, *Faecalibacterium*, and *Rothia* species (70). Another study reported lower relative abundance of *Citrobacter*, *Oscillospira*, *Lactococcus*, and *Dorea* in stool samples collected at age 3–6 mo in children who had FA (milk, egg, peanut, soy, or other nut allergy) by the age of 3 y (71). In addition, *Firmicutes*, including *Clostridium*, were enriched in the gut microbiota of infants at age 3–6 mo whose milk allergy resolved by 8 y of age (72), suggesting a potential predictive role of gut microbiota composition for FA.

Interestingly, the specific microbiota signature can distinguish infants with IgE-mediated from non–IgE-mediated FA. Infants with IgE-mediated FA had increased concentrations of *(cluster I)* and *Anaerobacter* and decreased concentrations of *Bacteroides* and *Clostridium cluster XVIII*, with a positive correlation between *Clostridium sensu stricto* and serum...
sIgE (73). However, as with observational studies, it is not possible to assess causation between changes in microbial composition and FA (74). A study in adults with FA showed the opposite results with reduced Clostridiales, and increased Bacteroidales (75), suggesting that the changes observed in microbiota associated with allergy can be different depending on other factors such as age, ethnicity, geographical location, and lifestyle.

It is widely known that the early infant microbiota is influenced by several factors, including mode of birth, antibiotic use, and environmental exposures, that can contribute to the dysbiosis linked to allergy development (Figure 1) and would provide opportunities to develop strategies aimed at microbial modulation and decreasing the risk of FA (76).

C-section delivery and antibiotic exposition
Available evidence indicates that C-section is a possible risk factor for FA because the newborn infant bypasses the microbial exposure happening naturally during vaginal delivery, whereby a distinct gut microbiota is obtained (77). In general, infants born by C-section have lower concentrations of Bacteroides and lower diversity, which is a pattern also observed to precede the development of allergic symptoms in several studies (78). However, there is no clear evidence on C-section association with a higher risk of FA development, with studies producing contradictory results (79, 80). However, a 7-fold increased risk of parental-reported fish or nut allergy and a 4-fold increased risk of confirmed egg allergy were reported (81) in high-risk children born via C-section. C-section was found to be associated with other allergic diseases, such as allergic rhinitis (OR: 1.23; 95% CI: 1.12, 1.35), asthma (OR: 1.18; 95% CI: 1.05, 1.32), and allergic sensitization to foods (OR: 1.32; 95% CI: 1.12, 1.55) (82). Most of the C-sections are associated with antibiotic intrapartum. Antibiotic use (particularly cephalosporins and sulfonamides), including its frequency during pregnancy and first year of life, was linked with an increased risk of FA development (83), and is likely to reflect an indirect effect via infant gut microbiota dysbiosis (84, 85).

Breastfeeding practices
It has been shown that infants with CMA had an increased gut microbiota diversity and a higher prevalence of members belonging to the Lachnospiraceae family (Firmicutes phylum) compared with nonallergic infants (86). However, another study showed an inverse association between the early gut microbial diversity and the risk of allergic sensitization (87). A low gut microbiota richness, overrepresentation of Enterobacteriaceae, and underrepresentation of Bacteroidaceae (Bacteroidetes phylum) at 3 mo of age were associated with food sensitization in a subset of the CHILD study (68). Those associations were found in infants who were vaginally delivered, exclusively breastfed, and unexposed to antibiotics. Breastfeeding practices were associated with lower diversity and higher concentrations of Bifidobacterium breve and B. bifidum (Actinobacteria phylum), and the cessation of breastfeeding resulted in faster maturation of the gut microbiota, as marked by an increase in the members belonging to the Firmicutes phylum (88). However, formula-fed infants had a more diverse microbiota with higher proportions of Clostridium spp. (Firmicutes phylum), and Enterobacteriaceae members (Proteobacteria phylum), but with lower bacterial count (89). Recent studies have shown that breast milk with a reduced microbial richness in the first month of life could play an important role in allergy development during childhood (90). Thus, the protection against allergy development provided by human milk might be attributable to the effect on the infant gut microbiota or direct effects on immune system; however, further studies are needed to evaluate the effect of breastfeeding and milk-specific compounds on FA (91).

Environmental exposures
Associations between living in affluent countries and allergic disease development are well known, and FA is no exception to the rule. A higher socioeconomic status (92) or living in developed societies were associated with an increased risk of FA development, although it is possible that variations in frequencies of studies and methodological variation also contribute to these geographic variations (4). Researchers suggest that farming lifestyle exposes pregnant women and their offspring to a wide variety of microorganisms, which urban inhabitants lack. Data from 2 large, prospective cohorts showed that exposure to a greater variety of environmental microorganisms was associated with a reduced risk of asthma development in “Prevention of Allergy—Risk Factors for Sensitization Related to Farming and Anthroposophic Lifestyle” (PARSIFAL study) (OR: 0.62; 95% CI: 0.44, 0.89) and in Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community (GABRIEL) Advanced Study (OR: 0.86; 95% CI: 0.75, 0.99) (93).

Dietary Interventions
Macronutrient and micronutrient associations with FA
A recent systematic review suggested that supplementation with fish oil [a source of long-chain omega-3 (n–3) fatty acids] during pregnancy and lactation can reduce risk of allergic sensitization to egg (RR: 0.69; 95% CI: 0.53, 0.90; I² = 15%; absolute risk reduction: 31 cases per 1000; 95% CI: 10, 47) (94). The Grading of Recommendations Assessment, Development and Evaluation certainty of these findings was moderate. In addition, in vitro and in vivo studies have demonstrated that n–3 PUFAs can modulate the activity of dendritic cells, T cells, and IgE production by B cells, reducing allergic sensitization (95).

Although vitamin D deficiency was linked with the development of allergic diseases (96), data relevant for FA are limited. Vitamin D deficiency linked with GG genotype producing less vitamin D binding protein was associated with...
a higher prevalence of egg and peanut allergy in 1- and 2-year-olds (97). Use of vitamin D supplements during pregnancy to prevent FA was, however, unsuccessful, both in an RCT (RR: 1.92; 95% CI: 0.57, 6.50) (98) and a case-control study (OR: 1.50; 95% CI: 0.78, 2.88) (99). Supplementation during the first year of life resulted in a reduced risk of FA development during the first 12 mo of life (RR: 0.49, 95% CI: 0.27, 0.88) (99). However, the confidence in this estimate is also very low owing to indirectness of the evidence and risk of bias, as reported in a recent systematic review on the subject (100). Overall, there is currently not enough evidence to suggest that vitamin D supplements for pregnant and/or breastfeeding women or infants have an effect on FA development (39).

**Dietary interventions targeting microbiota modulation: prebiotics and probiotics**

Targeted and personalized nutrition is an emerging strategy to approach FA in early infancy including microbiome-modifying interventions with probiotics (Lactobacillus acidophilus LAVRI A1, Lacticaseibacillus rhamnosus GG), prebiotics (long-chain fructo-oligosaccharides, short-chain galacto-oligosaccharides), and human milk oligosaccharides (2’-fucosyllactose, lacto-N-neotetraose) (101). The pathogenesis of FA in early infancy and other associated events such as dermatitis or asthma are still largely unknown, but increasing evidence suggests that they are associated with a perturbation of the gut microbiome, or microbial dysbiosis, leading to alterations in the immune system that could influence the occurrence of FA (102). In addition, FA derives from a defect in immune tolerance mechanisms. Immune tolerance is modulated by gut microbiota composition and function. Therefore, the potential use of probiotics has been highlighted to counteract microbial dysbiosis linked to FA and boost microbially modulated tolerance because evidence has pointed to the gut microbiota on regulatory T-cell (Treg) proliferation and function (120,121). In particular, the effect of butyrate on Treg differentiation would include the control of cellular metabolism and the G-protein-coupled receptor signaling pathways (118), and involve strong epigenetic regulation of T-cell differentiation (117). The mechanisms involved in SCFA regulation of T-cell differentiation would include the control of cellular metabolism and the G-protein-coupled receptor signaling pathways (118), and involve strong epigenetic regulation of T-cell differentiation through inhibition of histone deacetylases (102). In particular, the effect of butyrate on Treg differentiation could be through the increase of histone H3 acetylation in the FOXP3 locus (117), and propionate seems to increase the expression of FOXP3 and IL10 (119). These results could explain the benefits of dietary fiber and bacteria, such as Akkermansia muciniphila, Fecalibacterium prausnitzii, Eubacterium, Bifidobacterium, Clostridium, and Ruminococcus, typical SCFA producers, that can increase colonic luminal SCFA concentrations and modulate the immune system response (120, 121).

**Evidence for the Role of Microbial Metabolites in FA**

Increasing data are showing the key role of metabolites in the host–microbe interaction as messengers and signals between the microbiota and the immune system with an impact on human health. A comprehensive understanding of how microbiota-derived metabolites influence the human immune system and health is critical for the rational design of therapies for microbiota-driven diseases (110). Different dietary patterns change the proportions and type of microbial groups, influencing host exposure to microbial metabolites (111), which in turn produce epigenetic changes. Although no data are available for infants in their first year of life, in older children and adults, a balanced low-fat and high-fiber diet could be important in preventing perturbation of the gut microbiome and preserving a functional immune system (112). Little is known about the role of microbial metabolites in FA but evidence is showing the impact of diet including prebiotics on the production of microbial metabolites such as SCFAs, polyamines, and even other compounds as toxins (LPS, staphylococcal enterotoxin B, etc.).

**SCFAs**

Metabolites produced by intestinal microbiota, and in particular SCFAs, play a critical role in mediating the effect of the gut microbiota on regulatory T-cell (Treg) proliferation and differentiation both in vitro and in vivo (113). The molecular mechanisms for this are not clearly elucidated but butyrate can suppress NF-κB and STAT1 activation and induce differentiation of colonic Treg cells by enhanced histone acetylation (113–116). Moreover, these effects are not confined to the gastrointestinal tract, and both butyrate and propionate have been reported to influence peripheral Treg development (117). The mechanisms involved in SCFA regulation of T-cell differentiation would include the control of cellular metabolism and the G-protein-coupled receptor signaling pathways (108), and involve strong epigenetic regulation through inhibition of histone deacetylases (102). In particular, the effect of butyrate on Treg differentiation could be through the increase of histone H3 acetylation in the FOXP3 locus (117), and propionate seems to increase the expression of FOXP3 and IL10 (119). These results could explain the benefits of dietary fiber and bacteria, such as Akkermansia muciniphila, Fecalibacterium prausnitzii, Eubacterium, Bifidobacterium, Clostridium, and Ruminococcus, typical SCFA producers, that can increase colonic luminal SCFA concentrations and modulate the immune system response (120, 121).

Some specific SCFAs have been reported to influence FA. In detail, butyrate has a well-known inhibitory effect on
| Strain(s) | No. subjects | Intervention time | Target | Outcome(s) | Study type | Reference |
|-----------|--------------|-------------------|--------|------------|------------|-----------|
| **Clinical studies** | | | | | | |
| Lactobacillus GG | 100 infants diagnosed with CMA | 4 wk | Management of CMA | Significant improvement in symptoms of infants diagnosed with CMA | Randomized, double-blind, placebo-controlled study | (168) |
| Synbiotic formula with a combination of Bifidobacterium breve M-16V and chicory-derived neutral oligofructose, long-chain inulin | 122 infants | 8 wk | Management of severe or complex non-IgE-mediated CMA | ↑% of Bifidobacterium and ↓% of Eubacterium rectale/Clostridium coccoides group in the test group | Double-blind, randomized clinical trial with nonrandomized breastfed reference group | (169) |
| Lactobacillus rhamnosus and Bifidobacterium animalis ssp. lactis | 290 infants aged ~1 mo | 6 mo | Allergic diseases and sensitization | ↓Incidence of eczema | Randomized, double-blind, placebo-controlled intervention | (170) |
| Amino acid–based formula (AAF) with fructo-oligosaccharides and Bifidobacterium breve M-16V Lactobacillus rhamnosus GG; L. plantarum LC705 (DSM 7061), Bifidobacterium breve BB9 (DSM 13,692), and Propionibacterium freudenreichii ssp. shermanii JS (DSM 7076) | 51 infants aged <13 mo | 8 wk | Infant intervention for maternal-infant intervention | ↑Incidence of eczema in the AAF with probiotic and probiotic | Randomized, double-blind, placebo-controlled intervention | (109) |
| Maternal-infant intervention Follow-up until 5 y | | | | | | |
| Meta-analyses | | | | | | |
| Different strains | 10 RT; n = 845 infants | Different intervention times | Management of infants with suspected/proven CMA | No impact on hematochezia in confirmed CMA, probiotics | Meta-analysis | (172) |

(Continued)
| Strain(s) No. subjects Intervention time | Outcome(s) | Study type | Reference |
|-----------------------------------------|------------|------------|-----------|
| Single or multiple organisms, given as capsules, powder, or part of a drink or infant formula milk | Maternal-infant intervention | Allergyprevention | ↓ Risk of eczema and/or atopiceczema at age ≤4y ↓ Allergic sensitization to cow milk at age 1-2y ↓ Risk of food hypersensitivity | Systematic review and meta-analysis (94) |
| Combination of lactobacilli and bifidobacteria | Maternal-infant intervention | Allergyprevention | ↓ Risk of atopic eczema ↓ Risk of food hypersensitivity No impact on asthma, wheezing, or rhinoconjunctivitis | Systematic review and meta-analysis (173) |
| Combination of lactobacilli and bifidobacteria | Maternal intervention during pregnancy | Allergyprevention | ↓ Risk ratio for eczema | Meta-analysis (174) |

**Other microbial metabolites**

It has been suggested that some other microbial metabolites such as staphylococcal enterotoxin B could act as adjuvants of food allergens during simultaneous exposure via skin (74). *Staphylococcus aureus* colonisation of the skin has been associated with FA to peanut, egg white, and cow milk in patients with atopic dermatitis, and would be associated with skin barrier dysfunction and immune system dysregulation (124). Bacterial LPSs are strong immunostimulants that can induce tolerance at certain doses (125). Their role in allergy seems to be conditioned by the timing of exposure, the presence of pre-existing disease, and polymorphisms in the genes that encode endotoxin receptors (126). Evidence in humans is unclear but results from animal studies indicate LPS might prevent adverse IgE-mediated reactions by regulation of type 2 helper T-cell responses (127) and suppression of mast cell responses (128).

There is substantial evidence that intestinal bacteria can produce significant amounts of folate as well as other B vitamins complementing the dietary intake (129), including generally recognized beneficial microorganisms such as bifidobacteria and lactic acid bacteria (115). These B vitamins, and particularly folate, play a crucial role in epigenetic regulation as donors of methyl groups for DNA, RNA, and protein methylation (130, 131). Folate-induced changes in DNA methylation can modify gene expression in helper T cells (132), which has been proposed as a plausible mechanism underlying associations between folate and several diseases such as asthma (129), child wheeze (133), and allergy (134). For FA, it is still largely underexplored with contradictory results depending on the studies (132). Most of the few studies conducted to date suggest that maternal folate exposure is not associated with the development of FA (132). However, a retrospective study suggested that maternal folic acid supplementation in dosages higher than recommended might be a risk factor for allergy development (135).

Emerging evidence on the role of biotinylation upon immune function (136–138) and microbial metabolites such as polyamines (139–143) indicate potential further links between the gut microbiome and allergy by epigenetic regulation of genes modulating the activity of T and B lymphocytes, and proinflammatory cytokine expression (111, 136–144).
Recommendation/Guidance for Future Research

FA research is now experiencing an exciting new era thanks to advances on immunological, microbiological, and epigenetic factors and their integration, increasing knowledge of risk factors and potential biomarkers. However, limited data are available to identify potential biomarker or biomarker combinations determining a risk reduction in FA. The EAAACI has recently published a systematic review as a source of evidence to support the development of FA prevention guidelines (39). This systematic review included 46 intervention studies to reduce the risk of FA in infancy (≤1 y) or early childhood. Different interventions during pregnancy, lactation, and infancy, including dietary avoidance of food allergens, vitamin supplements, fish oil, probiotics, prebiotics, symbiotics, and emollients, were included. Results showed that interventions have little or no effect in preventing FA, but the evidence is very uncertain. The systematic review concluded that most of the evidence has been published in the last 10 y, and still no clear data are available on preventing FA. There is a need to validate the potential benefits of early introduction of food allergens in a wider range of populations. Furthermore, there is a lack of studies analyzing serial and longitudinal biomarkers from birth up to adulthood, and clear biomarkers have not been identified until now. Promising potential biomarkers associated with FA, such as the depletion of key microbial components (e.g., *Bifidobacterium* and *Bacteroides* genus) or methylation profiles in the *FOX3P* and *IL10* genes, should be deeply evaluated in future studies. To bridge the gap, more data are required on the maternal impact during gestation on fetal immune regulation as well as the immunometabolic profile of breast milk composition (immune cells, cytokines, hormones). There are also a limited number of studies focusing on immunology, microbiome, and diet, but few assess across the board. More cohort and intervention studies are needed to confirm which methylation profiles are suitable as biomarkers to monitor risk reduction of FA. Thus, designing nutritional intervention trials aimed at risk reduction of FA, or induction of tolerance, could need stratification based on specific risk factors to determine a design that is still feasible to execute. Indeed, the low incidence of oral food challenge–confirmed FA in the general population requires high numbers of infants to be able to detect a significant effect of an intervention. This review of currently available and emerging biomarkers linked to allergy can inform the design of future intervention studies. The available literature suggests that a highly collaborative approach spanning nutritional, genetic, and microbial biomarkers will be valuable in identifying panels of biomarkers that best predict FA, its severity, or its remission.

Acknowledgments

We thank Professor Philip Calder (University of Southampton, United Kingdom), Dr Jalil Benyacoub (Nestlé Health Science, Switzerland), Dr Stein-Erik Birkeland (Tine SA R&D, Norway), Dr Bruno Pot (Yakult Europe BV, The Netherlands), Dr Patrizia Bohnhorst (Procter & Gamble, Germany), Dr Elizabeth Forbes-Blom (Nestlé Research Center, Switzerland), and Professor Ascensión Marcos (ICTAN-CSIC, Spain) for their contributions to the discussions that form the basis of this article and their help in the reviewing phase. Dr Simon Bourdoux and Mr Adam Coventry (ILSI Europe, Belgium) coordinated the work of authors and facilitated meetings and discussions.

The authors’ responsibilities were as follows—CEC, DM, LU, CG-G, MCC: wrote and revised the manuscript; LL, TR, SS, MT: assisted the previously cited authors in designing the structure of the manuscript and in reviewing the final content; and all authors: read and approved the final manuscript.

References

1. Waserman S, Bégin P, Watson W. IgE-mediated food allergy. Allergy Asthma Clin Immunol 2018;14:55.
2. DunnGalvin A, Blumchen K, Timmermans F, Regent L, Schnadt S, Podestà M, Sánchez Á, Courpatier P, Feeney M, Hjorth B, et al. APPEAL-1: a multiple country European survey assessing the psychosocial impact of peanut allergy. Allergy 2020;75(11):2899–908.
3. Bärler LA, Chadha AS, Doshi P, O’Dwyer L, Gupta RS. Economic burden of food allergy: a systematic review. Ann Allergy Asthma Immunol 2019;122(4):373–380.e1.
4. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, Dubois AE, Halten S, Hoffmann-Sommergruber K, Poulsen LK, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy 2014;69(1):62–75.
5. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69(3):89–95.
6. European Commission. Regulation (EC) no 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Official Journal of the European Union 2006;404:9–25.
7. Anvari S, Miller J, Yeh CY, Davis CM. IgE-mediated food allergy. Clin Rev Allergy Immunol 2019;57(2):244–60.
8. Berin MC, Sampson HA. Food allergy: an enigmatic epidemic. Trends Immunol 2013;34(8):390–7.
9. Gelincik A, Büyüköztürk S, Gül H, İşik E, İşsever H, Özeker F, Çalışakoğlu B, Dal M, Ayvaz Ö, Gönçü G, et al. Confirmed prevalence of food allergy and non-allergic food hypersensitivity in a Mediterranean population. Clin Exp Allergie 2008;38(8):1333–41.
10. Pyhönen K, Hiltunen L, Kaila M, Nayha S, Laara E. Heredity of food allergies in an unselected child population: an epidemiological survey from Finland. Pediatr Allergy Immunol 2011;22(1 Pt 2):e124–32.
11. Sasaki M, Peters RL, Koplin JF, Field MJ, McWilliam V, Sawyer SM, Vullermin PJ, Pezic A, Gurrin LC, Douglass JA, et al. Risk factors for food allergy in early adolescence: the schoolnurts study. J Allergy Clin Immunol Pract 2018;6(2):496–505.
12. Venter C, Hasan Arshad S, Grundy J, Pereira B, Bernie Clayton C, Voigt K, Higgins B, Dean T. Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. Allergy 2010;65(1):103–8.
13. Venter C, Patil V, Grundy J, Glasbe y G, Twiselton R, Arshad SH, Dean T. Prevalence and cumulative incidence of food hyper-sensitivity in the first 10 years of life. Pediatr Allergy Immunol 2016;27(5):452–8.
14. Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Higgins B, Arshad SH, Dean T. Prevalence and cumulative incidence of food hypersensitivity in the first 3 years of life. Allergy 2008;63(3):354–9.
15. Bonnelykke K, Matheson MC, Pers TH, Granell R, Strachan DP, Alves AC, Linneberg A, Curtin JA, Warrington NM, Standl M, et al.
Meta-analysis of genome-wide association studies identifies ten loci influencing allergic sensitization. Nat Genet 2013;45(8):902–6.

16. Hong X, Hao K, Ladd-Acosta C, Hansen KD, Tsai H-J, Liu X, Xu X, Thornton TA, Caruso D, Keet CA, et al. Genome-wide association study identifies peanut allergy-specific loci and evidence of epigenetic mediation in US children. Nat Commun 2015;6(1):1–12.

17. Nicolau N, Poorafshar M, Murray C, Simpson A, Winell H,erry G, Harlin A, Woodcock A, Ahsledt S, Custovic A. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. J Allergy Clin Immunol 2010;125(1):191–7.e13.

18. Pyrhönen K, Nayha S, Kaila M, Hiltunen L, Laara E. Occurrence of parent-reported food hypersensitivities and food allergies among children aged 1–4 yr. Pediatr Allergy Immunol 2009;20(4):328–38.

19. Marenholz I, Grosche S, Kalb B, Ruschendorf F, Blumenen K, Schlags R, Harandi N, Price M, Hansen G, Seidenberg J, et al. Genome-wide association study identifies the SERPINB4 gene cluster as a susceptibility locus for food allergy. Nat Commun 2017;8(1):1056.

20. Kull I, Melen E, Alm J, Hallberg J, Svartengren M, van Hage M, Pershagen G, Wickman M, Bergstrom A. Breastfeeding in relation to asthma, lung function, and sensitization in young schoolchildren. J Allergy Clin Immunol 2010;125(5):1013–19.

21. Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. Lancet 1995;346(8982):1065–9.

22. Chalmers JR, Haines RH, Bradshaw LE, Montgomery AA, Thomas KS, Brown SJ, Ridd MJ, Lawton S, Simpson EL, Cork MJ, et al. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. Lancet 2020;395(10228):962–72.

23. Ricci JE, Patel BD, Lang IA, Kumari M, Frayling TM, Murray A, Melzer D. Filaggrin gene mutations are associated with asthma and eczema in later life. J Allergy Clin Immunol 2008;122(4):834–6.

24. Alam R, Abdolmaleky HM, Zhou JR. Microbiome, inflammation, epigenetic alterations, and mental diseases. Am J Med Genet B Neuropsychiatr Genet 2017;174(6):651–60.

25. Bowers EC, McCullough SD. Linking the epigenome with exposure effects and susceptibility: the epigenetic seed and soil model. Toxicol Sci 2017;155(2):302–14.

26. Freeland DMH, Manohar M, Andorf S, Hobson BD, Zhang W, Bowers EC, McCullough SD. Linking the epigenome with exposure effects and susceptibility: the epigenetic seed and soil model. Toxicol Sci 2017;155(2):302–14.

27. Lin PI, Shu H, Mersha TB. Comparing DNA methylation profiles across different tissues associated with the diagnosis of pediatric asthma. Sci Rep 2020;10(1):151.

28. Thibault AAH, Laprise C. Cell-specific DNA methylation signatures in asthma. Genes (Basel) 2019;10(11):932.

29. Victora CG, Bahl R, Barros AJD, França GVA, Horton S, Krasevec J, Marenholz I, Grosche S, Kalb B, Ruschendorf F, Blumenen K, Schlags R, Harandi N, Price M, Hansen G, Seidenberg J, et al. Genome-wide association study identifies the SERPINB4 gene cluster as a susceptibility locus for food allergy. Nat Commun 2017;8(1):1056.

30. Pyrhönen K, Nayha S, Kaila M, Hiltunen L, Laara E. Occurrence of parent-reported food hypersensitivities and food allergies among children aged 1–4 yr. Pediatr Allergy Immunol 2009;20(4):328–38.

31. Marenholz I, Grosche S, Kalb B, Ruschendorf F, Blumenen K, Schlags R, Harandi N, Price M, Hansen G, Seidenberg J, et al. Genome-wide association study identifies the SERPINB4 gene cluster as a susceptibility locus for food allergy. Nat Commun 2017;8(1):1056.

32. VandenElsenLWJ, Garssen J, Burcelin R, Verhasselt V. Shaping the gut microbiota by breastfeeding: the gateway to allergy prevention? Front Pediatr 2019;7:47.

33. Van Odijk J, Kull I, Borres MP, Brandtzaeg P, Edberg U, Hanson LÅ, Host A, Kuitunen M, Olsen SF, Skerfving S, et al. Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966-2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. Allergy 2003;58(9):833–43.

34. Lucas A, Brooke OG, Morley R, Cole TJ, Bamford MF. Early diet of preterm infants and development of allergic or atopic disease: randomised prospective study. BMJ 1990;300(6728):837–40.

35. Mihrshahi S, Ampon R, Webb K, Almqvist C, Kemp AS, Hector D, Marks GB. The association between infant feeding practices and subsequent atopy among children with a family history of asthma. Clin Exp Allergy 2007;37(5):671–9.

36. Pesonen M, Kallio MJT, Ranki A, Siimes MA. Prolonged exclusive breastfeeding is associated with increased atopic dermatitis: a prospective follow-up study of unselected healthy newborns from birth to age 20 years. Clin Exp Allergy 2006;36(8):1011–18.

37. Munblit D, Perkin MR, Palmer DJ, Allen KJ, Boyle RJ. Assessment of evidence about common infant symptoms and cow's milk allergy. JAMA Pediatr 2020;174(6):599–608.

38. Boix-Amorós A, Collado MC, Van't Land B, Calvert A, Le Doare K, Garsen J, Hanna H, Khaleva E, Peroni DG, Geddes DT, et al. Reviewing the evidence on breast milk composition and immunological outcomes. Nutr Rev 2019;77(8):541–56.

39. de Silva D, Halken S, Singh C, Muraro A, Angier E, Arasi S, Arshad H, Beyer K, Boyle R, du Toit G, et al. Preventing food allergy in infancy and childhood: systematic review of randomised controlled trials. Pediatr Allergy Immunol 2020;31(7):813–26.

40. Munblit D, Boyle RJ. Modulating breast milk composition—the key to allergy prevention? Int Arch Allergy Immunol 2012;159(2):107–8.

41. Munblit D, Peroni DG, Boix-Amorós A, Hsu PS, Van't Land B, Gay MCL, Kolotilina A, Skevaki C, Boyle RJ, Collado MC, et al. Human milk and allergic diseases: an unsolved puzzle. Nutrients 2017;9(8):894.

42. Munblit D, Boyle RJ, Warner JO. Factors affecting breast milk composition and potential consequences for development of the allergic phenotype. Clin Exp Allergy 2015;45(3):583–601.

43. Munblit D, Treneva M, Peroni DG, Colicino S, Chow LY, Dissanayake S, Abrol P, Sheth S, Pampura A, Boner AL, et al. Colostrum and mature human milk of women from London, Moscow, and Verona: determinants of immune composition. Nutrients 2016;8(11):695.

44. Ruiz L, Espinosa-Martos I, García-Carral C, Manzano S, McGuire MK, Meehan CL, McGuire MA, Williams JE, Foster J, Sellen DW, et al. What's normal? Immune profiling of human milk from healthy women living in different geographical and socioeconomic settings. Front Immunol 2017;8:696.

45. Tomićić S, Johansson G, Voor T, Björkstén B, Böttcher MF, Jenmalm MC. Breast milk cytokine and IgA composition differ in Estonian and Swedish mothers—relationship to microbial pressure and infant allergy. Pediatr Res 2010;68(4):330–4.

46. Picariello G, De Cicco M, Nocerino R, Paparo L, Mamone G, Addeo F, Berni Canani R. Excretion of dietary cow's milk-derived peptides into breast milk. Front Nutr 2019;6:25.

47. Gouw JW, Jo J, Meulenbroek L, Heijer T, Kremer E, Sandalova E, Knaul AC, Jeurnink PV, Garsen J, Ruijter E, et al. Identification of peptides with tolerogenic potential in a hydrolysed whey-based infant formula. Clin Exp Allergy 2018;48(10):1345–53.

48. Boyle RJ, Ierodiakonou D, Khan T, Chivinge I, Robinson Z, Geoghegan N, Jarrold K, Afentouli T, Reeves T, Cunha S, et al. Hydrolyzed formula and risk of allergic or autoimmune disease: systematic review and meta-analysis. BMJ 2016;352:i659.

49. Osborn DA, Sinn JKH, Jones LJ. Infant formulas containing hydrolyzed protein for prevention of allergic disease. Cochrane Database Syst Rev 2018;10(10):CD003664.

50. Knol EF, de Jong NW, Ulfman LH, Tiemessen MM. Management of cow's milk allergy from an immunological perspective: what are the options? Nutrients 2019;11(11):2734.
Canadian Society for Allergy and Clinical Immunology. J Allergy Clin Immunol Pract 2021;9(1):22–43.e4.

52. Greer FR, Sicherer SH, Burks AW. The effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, hydrolyzed formulas, and timing of introduction of allergenic complementary foods. Pediatrics 2019;143(4):e20190281.

53. Urashima M, Mandhane PJ, Turvey SE, Subbarao P, Becker AB, et al. Infant gut microbiota and food sensitization: associations in the first year of life. Clin Exp Allergy 2015;45(3):632–43.

59. Kozyrskyj AL. Can we predict future allergies from our infant gut microbiota? Expert Rev Respir Med 2015;9(6):667–70.

60. Arrieta M-C, Stensma LT, Dimitriou PA, Torshon L, Russell Y, Yurist-Dutsch S, Kuzeljevic B, Gold MJ, Britton HM, Lefebvre DL, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. Sci Transl Med 2015;7(307):307ra132.

61. Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton N, Tachimoto H. Primary prevention of cow's milk sensitization and food allergy by avoiding supplementation with cow's milk formula at birth: a randomized control trial. JAMA Pediatr 2019;173(12):1137–45.

62. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, Brough H, Marris T, Radulovic S, Craven J, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl J Med 2016:374(18):1733–43.

63. Elbert NJ, Kiefte-de Jong JC, Voortman T, Nijsten TE, De Jong NW, Jaddoe VVV, De Jongste JC, Van Wijk RG, Duijts L, Pasmans S. Allergenic food introduction and risk of childhood atopic diseases. PLoS One 2017;12(11):e0187999.

64. Elbert NJ, Kiefte-de Jong JC, Voortman T, Nijsten TE, De Jong NW, Jaddoe VVV, De Jongste JC, Van Wijk RG, Duijts L, Pasmans S. Allergenic food introduction and risk of childhood atopic diseases. PLoS One 2017;12(11):e0187999.

65. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, Brough H, Marris T, Radulovic S, Craven J, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl J Med 2016;374(18):1733–43.

66. Elbert NJ, Kiefte-de Jong JC, Voortman T, Nijsten TE, De Jong NW, Jaddoe VVV, De Jongste JC, Van Wijk RG, Duijts L, Pasmans S. Allergenic food introduction and risk of childhood atopic diseases. PLoS One 2017;12(11):e0187999.

67. Zhao W, He Ho, Bunyavanich S, Zhou Y, O'Connor G, Sandel M, Bacharier LB, Zeiger R, Sodergren E, et al. A prospective microbiome-wide association study of food sensitization and food allergy in early childhood. Allergy 2018;73(1):145–52.

68. Azad MB, Konya T, Guttmann DS, Field CJ, Sears MR, HayGlas KT, Mandhane PJ, Turvey SE, Subbarao P, Becker AB, et al. Infant gut microbiota and food sensitization: associations in the first year of life. Clin Exp Allergy 2015;45(3):632–43.

69. Kozyrskyj AL. Can we predict future allergies from our infant gut microbiota? Expert Rev Respir Med 2015;9(6):667–70.

70. Arrieta M-C, Stensma LT, Dimitriou PA, Torshon L, Russell Y, Yurist-Dutsch S, Kuzeljevic B, Gold MJ, Britton HM, Lefebvre DL, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. Sci Transl Med 2015;7(307):307ra132.

71. Savage JH, Lee-Sarwar KA, Sordillo J, Bunyavanich S, Zhou Y, O'Connor G, Sandel M, Bacharier LB, Zeiger R, Sodergren E, et al. A prospective microbiome-wide association study of food sensitization and food allergy in early childhood. Allergy 2018;73(1):145–52.

72. Bunyavanich S, Shen N, Grishin A, Wood R, Burks W, Dawson P, Jones SM, Leung DYM, Sampson H, Håcker S, et al. Early-life gut microbiome composition and milk allergy resolution. J Allergy Clin Immunol 2016;138(1):1122–30.

73. Ling Z, Li Z, Liu X, Cheng Y, Luo Y, Tong Y, Yuan L, Wang Y, Sun J, Li L, et al. Altered faecal microbiota composition associated with milk allergy in infants. Allergy 2014;69(9):922–27.

74. Beneé S, Blázquez AB, Chiang D, Tordesillas I, Berin MC. The rise of food allergy: environmental factors and emerging treatments. EBioMedicine 2016;7:27–34.

75. Hua X, Goedert J, Pu A, Yu G, Shi J. Allergy associations with the adult fecal microbiota. EBioMedicine 2016;3:172–9.

76. Renn H, Skevaki C. Early life microbial exposures and allergy risks: opportunities for prevention. Nat Rev Immunol 2021;21(3):177–91.

77. Domínguez-Bello MG, De Jesus-Laboy KM, Shen N, Cox LM, Amir A, Gonzalez A, Bokulich NA, Song SJ, Hoashi M, Rivera-Vinas JI, et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. Nat Med 2016;22(3):250–3.

78. Sha SU, Yuan AWT, Woo E, Chu KH, Kwan HS, Yang GX, Yang Y, Leung PSC. Microbiota and food allergy. Clin Rev Allergy Immunol 2016;51(1):83–97.

79. Paphathoma E, Triga M, Fouzas S, Dimitriou G. Cesarean section delivery and development of food allergy and atopic dermatitis in early childhood. Pediatr Allergy Immunol 2016;27(4):419–24.

80. Pyrénönen K, Nayha S, Hiltunen L, Laara E. Cesarean section and allergic manifestations: insufficient evidence of association found in population-based study of children aged 1 to 4 years. Acta Paediatr 2013;102(10):982–9.

81. Eggesbo M, Botten G, Stigum H, Naftaad P, Magnus P. Is delivery by cesarean section a risk factor for food allergy? J Allergy Clin Immunol 2003;112(2):420–6.

82. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: meta-analyses. Clin Exp Allergy 2008;38(4):634–42.

83. Love BL, Mann JR, Hardin JW, Lu ZK, Cox C, Amrol DJ. Antibiotic prescription and food allergy in young children. Allergy Asthma Clin Immunol 2016;12(1):41.

84. Huang YI, Marsland BJ, Bunyavanich S, O’Mahony L, Leung DYM, Muraro A, Flenser TA. The microbiome in allergic disease: current understanding and future opportunities—2017 PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology. J Allergy Clin Immunol 2017;139(4):1099–110.

85. Kim S, Covington A, Pamer EG. The intestinal microbiota: antibiotics, colonization resistance, and enteric pathogens. Immunol Rev 2017;279(1):90–105.

86. Canani RB, Sangwan N, Stelka AF, Nocerino R, Paparo L, Aitoro R, Calignano A, Khan AA, Gilbert JA, Nagler CR. Lactobacillus rhamnosus GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants. ISME J 2016;10(3):742–50.

87. Bisgaard H, Li N, Bonnelykke K, Chawes BLK, Skov T, Paludan-Müller G, Stokholm J, Smith B, Krogfelt KA. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. J Allergy Clin Immunol 2011;128(3):646–52.e5.
88. Stewart CJ, Ajmani NJ, O’Brien JL, Hutchinson DS, Smith DP, Wong MC, Ross MC, Lloyd RE, Dodapaneni H, Metcalf GA, et al. Temporal development of the gut microbiome in early childhood from the TEDDY study. Nature 2018;562(7728):583–8.

89. Bezirtzoglou E, Tsitsias A, Welling GW. Microbiota profile in feces of breast-and formula-fed newborns by using fluorescence in situ hybridization (FISH). Anaerobe 2011;17(6):478–82.

90. Dzidic M, Mira A, Artacho A, Abrahamsson TR, Jenmalm MC, Collado MC. Allergy development is associated with consumption of breastmilk with a reduced microbial richness in the first month of life. Pediatr Allergy Immunol 2020;31(3):250–7.

91. Jarvinen KM, Martin H, Oyoshi MK. Immunomodulatory effects of breast milk on food allergy. Ann Allergy Asthma Immunol 2019;123(2):133–43.

92. Kots D, Simpson CR, Sheikh A. Incidence, prevalence, and trends of general practitioner-recorded diagnosis of peanut allergy in England, 2001 to 2005. J Allergy Clin Immunol 2011;127(3):623–30.e1.

93. Ege MJ, Mayer M, Normand AC, Genuite J, Cookson W, Braun-Fahrlander C, Heederik D, Piirroux R, Von Mutius E. Exposure to environmental microorganisms and childhood asthma. N Engl J Med 2011;364(8):701–9.

94. García-Larsen V, Ierodiakonou D, Jarrold K, Cunha S, Chivinge J, Robinson Z, Geoghegan N, Ruparelia A, Devani P, Trivella M, et al. Diet during pregnancy and infancy and risk of autoimmune disease: a systematic review and meta-analysis. PLoS Med 2018;15(2):e1002507.

95. Hoppenbrouwers T, Cvejić Hogervorst JH, Garssen J, Wichers HJ, Mazzotta E, Michiels K. Microbiota and the gut microbiome: mediators of the gut-brain axis in food allergy. Front Immunol 2019;10:1118.

96. Aryan Z, Rezaei N, Camargo CA. Vitamin D status, aeroallergen sensitization, and allergic rhinitis: a systematic review and meta-analysis. Int Rev Immunol 2017;36(1):41–53.

97. Koplin JJ, Suaini NH, Vuillermin P, Ellis JA, Panjari M, Ponsoby AL, Peters RL, Matheson MC, Martino D, Dang T, et al. Polyphenol polymorphism affecting vitamin D-binding protein modify the relationship between serum vitamin d (25(OH)D3) and food allergy. J Allergy Clin Immunol 2016;137(2):500–6.e4.

98. Goldring ST, Griffiths CJ, Martineau AR, Robinson S, Yu C, Poulton S, Devlin RB, Fredericks K, et al. Prenatal vitamin D supplementation and child respiratory health: a randomised controlled trial. PLoS One 2013;8(6):e66627.

99. Allen KJ, Koplin JJ, Ponsoby AL, Gurrin LC, Wake M, Vuillermin P, Martin P, Matheson M, Lowe A, Robinson M, et al. Vitamin D insufficiency is associated with challenge-proven food allergy in infants. J Allergy Clin Immunol 2013;131(4):1109–16.e6.

100. Yepes-Nuñez JJ, Bro˙zek JL, Fiocchi A, Pawankar R, Cuello-García C, Zhang Y, Morgano GP, Agarwal A, Gandhi S, Terracciano L, et al. Diet during pregnancy and infancy and risk of allergic or autoimmune disease: a systematic review and meta-analysis. PLoS Med 2011;364(8):701–9.

101. Heine RG. Food allergy prevention and treatment by targeted nutrition. Ann Nutr Metab 2018;72(Suppl.3):33–45.

102. Truth T, Höffner-Sommergruber K, Schmitt J, Tandoi L, Rizzardi S, Boehm G. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. J Nutr 2008;138(6):1091–5.

103. Arslanoglu S, Moro GE, Schmitt J, Tandoi L, Rizzardi S, Boehm G. A specific probiotic-containing amino acid-based formula restores gut microbiota in non-IgE mediated cow’s milk allergic infants: a randomized controlled trial. Clin Transl Allergy 2019;9(1):27.

104. Levy M, Thaiss CA, Elinav E. Metabolites: messengers between the microbiota and the immune system. Genes Dev 2016;30(14):1589–97.

105. Bullar MAJ, Fu BC, Diet, the gut microbiome, and epigenetics. Cancer J 2014;20(3):170–5.

106. Fiocchi A, Pawankar R, Cuello-García C, Ahn K, Al-Hammadi S, Agarwal A, Beyer K, Burks W, Canoniga GW, Ebsahe M, et al. World Allergy Organization-McMaster University guidelines for allergic disease prevention (GLAD-P): probiotics. World Allergy Organ J 2015;8(1):4.

107. Arslanoglu S, Moro GE, Schmitt J, Tandoi L, Rizzardi S, Boehm G. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. J Nutr 2008;138(6):1091–5.

108. Moro G, Arslanoglu S, Stahl B, Jelinek J, Wahn U, Boehm G. A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. Arch Dis Child 2006;91(10):814–19.

109. Wopereis H, Van Ampting MTJ, Cetinayruek-Yavuz A, Slump R, Candy DCA, Butt AM, Peroni DG, Vandenplas Y, Fox AT, Shah N, et al. Specific symbiotic-containing amino acid-based formula restores gut microbiota in non-IgE mediated cow’s milk allergic infants: a randomized controlled trial. Clin Transl Allergy 2019;9(1):27.

110. Levy M, Thaiss CA, Elinav E. Metabolites: messengers between the microbiota and the immune system. Genes Dev 2016;30(14):1589–97.

111. Bullar MAJ, Fu BC, Diet, the gut microbiome, and epigenetics. Cancer J 2014;20(3):170–5.

112. Brown K, DeCoffe D, Molcan E, Gibson DL. Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. Nutrients 2012;4(8):1095–119.

113. Luo A, Leach ST, Barres R, Hesson LB, Grimm MC, Simar D. The microbiota and epigenetic regulation of T helper 17/regulatory T cells: in search of a balanced immune system. Front Immunol 2017;8:417.

114. Bourassa MW, Alim I, Bullman SJ, Ratan RR. Butyrate, neuroepigenetics and the gut microbiome: can a high fiber diet improve brain health? Neurosci Lett 2016;625:56–63.

115. Qin Y, Wade PA. Crosstalk between the microbiome and epigenome: messages from bugs. J Biochem 2018;163(2):105–12.

116. Tzur G, Levy A, Meiri E, Barad O, Spector Y, Bentwich Z, Mizrahi I, Katzellenbogen M, Ben-Shushan E, Reubinoff BE, et al. MicroRNA expression patterns and function in endodermal differentiation of human embryonic stem cells. PLoS One 2008;3(11):e3726.

117. Arpaia N, Campbell C, Fan X, Dikty S, Van Der Veeken J, Deroos P, Liu H, Cross JR, Pfeffer K, Coffer PJ, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature 2013;504(7480):451–5.

118. Kim CH, Park J, Kim M. Gut microbiota-derived short-chain fatty acids, T cells, and inflammation. Immune Network 2014;14(6):277.

119. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-Y M, Glickman JN, Garrett WS. The microbial metabolites, short-chain fatty acids, regulate colonic T reg cell homeostasis. Science 2013;341(6145):569–73.

120. Baxter NT, Schmidt AW, Venkataraman A, Kim KS, Waldron C, Schmidt TM. Dynamics of human gut microbiota and short-chain fatty acids in response to dietary interventions with three fermentable fibers. mBio 2019;10(1):e02566–18.

121. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes 2016;7(3):189–200.

122. Berni Canani R, De Filippis F, Nocerino R, Paparo L, Di Scala C, Cosenza L, Della Gatta G, Calignano A, De Caro C, Laiola M, et al. The gut microbiota and the immune system. Genes Dev 2016;30(14):1589–97.

123. Sandin A, Bråbäck L, Norin E, Björkstén B. Faecal short chain fatty acid pattern and allergy in early childhood. Acta Paediatr 2009;98(5):823–7.

124. Jones AL, Curran-Edgett D, Leung DYM. Food allergy is associated with Staphylococcus aureus colonization in children with atopic dermatitis. J Allergy Clin Immunol 2016;137(4):1247–8.e3.
125. Wassenaar TM, Zimmermann K. Lipopolysaccharides in food, food supplements, and probiotics: should we be worried? Eur J Microbiol Immunol 2018;8(3):63–9.

126. Williams IK, Ownby DR, Malarik MJ, Johnson CC. The role of endotoxin and its receptors in allergic disease. Ann Allergy Asthma Immunol 2005;94(3):323–32.

127. Tori I, Shimizu S, Daimon T, Shinohara Y, Kudo T, Sato A, Tsuimura T. Exposure to high doses of lipopolysaccharide during ovalbumin sensitization prevents the development of allergic Th2 responses to a dietary antigen. J Toxicol Pathol 2014;27(4):205–13.

128. Wang N, McLelll M, Dang A, Yamani A, Waggoner I, Vanoni S, Noah T, Wu D, Kordowski A, Köh l J, et al. Lipopolysaccharide suppresses IgE-mast cell-mediated reactions. Clin Exp Allergy 2017;47(12):1574–85.

129. Kok DE, Steegenga WT, McKay JA. Folate and epigenetics: why we should not forget bacterial biosynthesis. Epigenomics 2018;10(9):1147–50.

130. Crider KS, Yang TP, Berry RJ, Bailey LB. Folate and DNA methylation: a review of molecular mechanisms and the evidence for folate’s role. Adv Nutr 2012;3(1):21–38.

131. McKay JA, Mathers JC. Diet induced epigenetic changes and their implications for health. Acta Physiologica 2011;202(2):103–18.

132. Brown SB, Reeves KW, Bertone-Johnson ER. Maternal folate exposure in pregnancy and childhood asthma and allergy: a systematic review. Nutr Rev 2014;72(1):55–64.

133. Roy A, Kocak M, Hartman TJ, Vereen S, Adgent M, Piyathilake T, Ali M, van den Biggelaar AHJ, Tulic MK. Presymptomatic diseases and prospects for management and prevention. Nutrients 2017;9(9):1–13.

134. Hesterberg RS, Cleveland JL, Epling-Burnette PK. Role of polyamines in immune cell functions. SciRep 2020;10(1):3552.

135. Buyuktiryaki B, Sahiner UM, Birben E, Tuncer A, Yakarisik T, Wu D, Kordowski A, Köhl J, et al. Lipopolysaccharide suppresses IgE-mast cell-mediated reactions. Clin Exp Allergy 2017;47(12):1574–85.

136. Bhat MI, Kapila R. Dietary metabolites derived from gut microbiota: with early childhood wheeze and atopic dermatitis. Pediatr Allergol Immunol 2018;29(2):144–50.

137. Elahi A, Sabui S, Narasappa NN, Agrawal S, Lambrecht NW, Agrawal S, Bhat MI, Kapila R. Dietary metabolites derived from gut microbiota: with early childhood wheeze and atopic dermatitis. Pediatr Allergol Immunol 2018;29(2):144–50.

138. Socha-Banasiak A, Kamer B, Gach A, Wysocka U, Jakubowski L, Czkwianianc E, Glowacka E, Czkwianianc E. Folate status, regulatory T cells and pregnancy – the effect on allergy development in children. Adv Nutr 2012;3(1):21–38.

139. Venkataraman D, Soto-Ramírez N, Kurukulaaratchy RJ, Holloway JW, Karmawa M, Ewart SL, Arshad SH, Erlewyn-Lajeunesse M. Filaggrin loss-of-function mutations are associated with food allergy and childhood atopic dermatitis. Pediatr Allergy Immunol 2014;134(4):876–82.e4.

140. Bhat MI, Kapila R. Dietary metabolites derived from gut microbiota: with early childhood wheeze and atopic dermatitis. Pediatr Allergol Immunol 2018;29(2):144–50.

141. McCabe LR, Parameswaran N. Advances in probiotic regulation of immune cell functions. SciRep 2020;10(1):3552.

142. Clark A, Mach N. Role of vitamin D in the hygiene hypothesis: the interplay between vitamin D, vitamin D receptors, gut microbiota, and immune response. Front Immunol 2016;7:627.

143. Buyuktiryaki B, Sahiner UM, Girgin G, Birben E, Soyer OU, Cakvaytar O, Cakvaytar O, Kaya Z, Aydogan S, Soyer OU, Buyuktiryaki B. Associations between milk and egg allergens and the IL1RA-DRB1/DQ polymorphism: a bioinformatics approach. Int Arch Allergy Immunol 2016;169(1):33–9.

144. Dimitrov I, Doytchinova I. Associations between milk and egg allergens and the IL1RA-DRB1/DQ polymorphism: a bioinformatics approach. Int Arch Allergy Immunol 2016;169(1):33–9.

145. Martino D, Neeland M, Dang T, Cobb J, Ellis J, Barnett A, Tang M, Vuillermin P, Allen K, Safery R. Epigenetic dysregulation of naïve CD4+ T-cell activation genes in childhood food allergy. Nat Commun 2018;9(1):3308.

146. Martino D, Neeland M, Dang T, Cobb J, Ellis J, Barnett A, Tang M, Vuillermin P, Allen K, Safery R. Epigenetic dysregulation of naïve CD4+ T-cell activation genes in childhood food allergy. Nat Commun 2018;9(1):3308.

147. Martino D, Neeland M, Dang T, Cobb J, Ellis J, Barnett A, Tang M, Vuillermin P, Allen K, Safery R. Epigenetic dysregulation of naïve CD4+ T-cell activation genes in childhood food allergy. Nat Commun 2018;9(1):3308.

148. Elahi A, Sabui S, Narasappa NN, Agrawal S, Lambrecht NW, Agrawal S, Bhat MI, Kapila R. Dietary metabolites derived from gut microbiota: with early childhood wheeze and atopic dermatitis. Pediatr Allergol Immunol 2018;29(2):144–50.

149. Ashu S, Gurrin L, Koplín J, Ponsóny AL, Allen KJ, et al. Blood DNA methylation biomarkers predict clinical reactivity in food-sensitized infants. J Allergy Clin Immunol 2015;135(5):1319–28.e12.

150. Martino D, Joo JE, Sexton-Oates A, Dang T, Allen K, Safery R, Prescott S. Epigenome-wide association study reveals longitudinally stable DNA methylation differences in CD4+ T cells from children with IgE-mediated food allergy. Epigenetics 2014;9(7):998–1006.

151. Petrus NCM, Henneman P, Venema A, Mul A, Van Sinderen F, Mertens T, Wu D, Kordowski A, Köhl J, et al. Lipopolysaccharide suppresses IgE-mast cell-mediated reactions. Clin Exp Allergy 2017;47(12):1574–85.

152. Martino D, Joo JE, Sexton-Oates A, Dang T, Allen K, Safery R, Prescott S. Epigenome-wide association study reveals longitudinally stable DNA methylation differences in CD4+ T cells from children with IgE-mediated food allergy. Epigenetics 2014;9(7):998–1006.
162. Hong X, Ladd-Acosta C, Hao K, Sherwood B, Ji H, Keet CA, Kumar R, Caruso D, Liu X, Wang G, et al. Epigenome-wide association study links site-specific DNA methylation changes with cow’s milk allergy. J Allergy Clin Immunol 2016;138(3):908–11.e9.

163. Van Bilsen JHM, Sienkiewicz-Szlapka E, Lozano-Ojalvo D, Willemsen LEM, Antunes CM, Molina E, Smit JJ, Wróblewska B, Wichers HJ, Knol EF, et al. Application of the adverse outcome pathway (AOP) concept to structure the available in vivo and in vitro mechanistic data for allergic sensitization to food proteins. Clin Trans Allergy 2017;7(1):13.

164. Paparo L, Nocerino R, Bruno C, Di Scala C, Cosenza L, Bedogni G, Di Costanzo M, Mennini M, D’Argenio V, Salvatore F, et al. Randomized controlled trial on the influence of dietary intervention on epigenetic mechanisms in children with cow’s milk allergy: the EPICMA study. Sci Rep 2019;9:2828.

165. Syed A, Garcia MA, Lyu SC, Bucayu R, Kohli A, Ishida S, Berglund JP, Tsai M, Mæcker H, O’Riordan G, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). J Allergy Clin Immunol 2019;133(2):500–10.e11.

166. Paparo L, Nocerino R, Cosenza L, Aitoro R, D’Argenio V, Del Monaco V, Di Scala C, Amoroso A, Di Costanzo M, Salvatore F, et al. Epigenetic features of FoxP3 in children with cow’s milk allergy. Clin Epigenetics 2016;8:86.

167. Alag A. Machine learning approach yields epigenetic biomarkers of food allergy: a novel 13-gene signature to diagnose clinical reactivity. PLoS One 2019;14(6):e0218253.

168. Basturk A, Isik İ, Atalay A, Yilmaz A. Investigation of the efficacy of Lactobacillus rhamnosus GG in infants with cow’s milk protein allergy: a randomised double-blind placebo-controlled trial. Probiotics Antimicrob Proteins 2020;12(1):138–43.

169. Fox AT, Wopereis H, Van Ampting MTJ, Oude Nijhuis MM, Butt AM, Peroni DG, Vandenplas Y, Candy DCA, Shah N, West CE, et al. A specific symbiotic-containing amino acid-based formula in dietary management of cow’s milk allergy: a randomized controlled trial. Clin Trans Allergy 2019;9:5.

170. Schmidt RM, Pilmann Laursen R, Bruun S, Larnkjær A, Mølgaard C, Michaelsen KF, Hest A. Probiotics in late infancy reduce the incidence of eczema: a randomized controlled trial. Pediatr Allergy Immunol 2019;30(3):335–40.

171. Kuitunen M, Kukkonen K, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Haahrela T, Savilahti E. Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. J Allergy Clin Immunol 2009;123(2):335–41.

172. Qamer S, Deshmukh M, Patole S. Probiotics for cow’s milk protein allergy: a systematic review of randomized controlled trials. Eur J Pediatr 2019;178(8):1139–49.

173. Zhang GQ, Hu HJ, Liu CY, Zhang Q, Shakya S, Li ZY. Probiotics for prevention of atopy and food hypersensitivity in early childhood: a PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2016;95(8):e2562.

174. Zuccotti G, Meneghin F, Aceti A, Barone G, Callegari ML, Di Mauro A, Fantini MP, Gori D, Indrio F, Maggio L, et al. Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis. Allergy 2015;70(11):1356–71.