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Asthma and Microbial Flora What is the Relation?

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ABSTRACT

It has been noticed that asthma is associated with changes in the microbiome (microbial flora) of the subject as early as the start of the atopic march in infancy. Increasing evidence suggests that the compositions of the lung and gut microbiomes determine the risk of asthma and allergies. Regulating the microbiome of the mother prenatal and the newborn postnatal seems to be the most promising approach in preventing or ameliorating atopy. Identification of populations at risk is of utmost importance to ensure primary prevention. Effective anti-viral therapies, targeting pathogenic bacteria within the nasopharyngeal microbiome during the first year, could represent a prophylactic approach to asthma.

KEYWORDS

Asthma; Microbiome; Microbial Flora; Atopy; Parasites.

INTRODUCTION

There is an increase in the prevalence of atopic disorders in infants and children in our developing countries since we started adopting 'Westernized life style" with different modifying diet pattern which affected our microbial flora diversity and composition, add to it the environmental changes. This change in composition of our microbial flora impaired our immune regulatory mechanism and immune tolerance to environment [1].

Asthma is defined as "the experience of a variable degree of airflow obstruction, breathlessness, with bronchial hyper responsiveness, associated with chronic airway inflammation and excessive mucus production". There is airway modulation and non-reversible changes of the bronchial tree. Airway remodeling can often cause irreversible airflow limitation and an increase of airway hyper responsiveness [2]. There are various specific and unspecific triggers which have been identified that can lead to an increase in inflammation, obstruction and symptoms.

Traditionally, asthma, especially allergic asthma, has been considered an inflammatory disease associated in an increase in TH2 cells, IgE antibodies, and accumulation of eosinophils in the lungs with goblet cell hyperplasia [3, 4]. Asthma is a complex syndrome which includes different phenotypes [4]. There are early-onset allergic asthma, late-onset eosinophilic asthma, exercise-induced asthma, obesity-related asthma and non-eosinophilic asthma [4, 5]. Lately it has been noticed that asthma in general is associated with changes in the microbiome (microbial flora) of the subject as early as the start of the atopic march in infancy [6].

Given that the microbial flora has been associated with communicable and non-communicable diseases, it would be essential to find a relation between microbiomes and asthma.

What is microbiome, microbiota or microbial flora?

Microbiota is "the ecological community of commensal, symbiotic and pathogenic microorganisms that literally share our body space". The Human Microbiome (all of our microbes'

genes) can be considered a counterpart to the human genome (all of our genes). The genes in our microbiome outnumber the genes in our genome by about 100 to 1 [7].

The microbial communities, particularly in the gut, play a key role in the development and maintenance of immune responses, protection from pathogenic organisms and counteract the inflammatory cytokines that are produced by pathogens, i.e. "Infection, inflammation & atopy" [8, 9].

Scholars distinguish between the concepts of microbiome and microbiota to separate the collective genomes of microorganisms from the microorganisms themselves, although the original definitions do not distinguish between them [10]. The adult human harbors approximately 100 billion bacteria in the intestine alone, and the microbiome accounts for about 90% of the cells in the human body. The human genome comprises about 21,000 (23000) genes that encode proteins [11]. In contrast, the microbiome may comprise approximately one to three million genes. The microbiome may be considered a "new organ system" because its existence and contributions to human health was uncovered by researchers between 15 and 20 years ago [12].

The composition and function of the microbiome of the human gut evolves during the first years of life and stabilizes within the first 3 years of age [13, 14]. The development of the gut microbiome is influenced by interactions between diet, environment, and host-microbe-associated factors. The gut microbiome plays a fundamental role in shaping host immunity by balancing the activities of Th-1 cells and Th-2 cells [15].

The microbiota can activate distinct tolerogenic dendritic cells in the gut and through this interaction can drive regulatory T-cell differentiation, which corrects the Th-2 immune skewing that is thought to occur at birth [16]. If appropriate immune tolerance is not established in early life and maintained afterward, it will represent a risk factor for the development of inflammatory, autoimmune, and allergic diseases [17]. The factors that affect and determine the microbial flora are: type of delivery being cesarean section/NVD, breastfeeding/bottle, timing of introduction of solid foods, and the use of antibiotics by the mother or infant during early 100 days of life [18]. All the factors mentioned affect the gut microbiome development and are associated with increased or decreased incidences of asthma and allergies [19].

Infants at one-month of age, who were colonized with Clostridium *difficile* after cesarean section, were found to have an increase in the risk of asthma at 6 years of age [20]. The gut microbiome, depending on the stimulus, has airway response when the microbiome is disrupted, toward either Th-1 cells (possibly suppressed in asthma and allergy) or Th-2 cells (enhanced in asthma and allergy) [21]. By controlling the activation of antigen-presenting dendritic cells in the gut, single bacterial species may regulate the differentiation of naïve T cells into regulatory T cells [22]. The lungs of the new-born infants were believed mistakenly for many years that they are sterile. Factors affecting early respiratory colonization are antibiotics, delivery method, chorioamnionitis/antenatal colonization, bowel colonization, nasopharyngeal colonization, and feeding methods. All these lead to neonatal and lung colonization which in turn have an impact as early respiratory colonization which lead to risk of bronchitis, long term risk of wheeze/asthma, mucosal immune modulation and risk of chronic lung disease especially in preterm infants [23]. In children with asthma, the bacterial load is significantly higher in the lung compared with healthy controls [24]. Airway microbiological diversity in the lungs was significantly greater in asthmatic children who demonstrated significant reduction in bronchial responsiveness after antibiotic treatment [25]. Six weeks of treatment of asthmatic patients with azithromycin reduces the relative abundance of: *Prevotella* from 4.54 to 3.43%, *Staphylococcus* from 10.49 to 4.59%, and *Haemophilus* from 10.74 to 3.28% [26].

Increasing evidence suggests that the compositions of the lung and gut microbiomes determine the risk of asthma and allergies. The hygiene hypothesis argues that the lack of early exposure to infectious agents, symbiotic microorganism's increases susceptibility to allergic diseases through insufficient stimulation of Th-1 cells, which cannot counterbalance the effects of Th-2 cells, leading to predisposition to allergic diseases [27].

The biodiversity hypothesis suggests that disturbances in the composition of the gut microbiome of citizens of western countries induced by antibiotics, diet, and lifestyle disrupt the mechanisms of mucosal immunological tolerance. The biodiversity hypothesis extends the hygiene hypothesis by stating that the gut microbiome interacts with the immune system to maintain the efficiency of the immune system [28].

Factors affecting diversity are diet, host genetics, treatment medication, environment, immunity and previous infection. Evidence indicates that the diversity of the body's microbiota is negatively associated with the risk of developing asthma and allergy. The biodiversity and microbiota hypotheses argue that changes in how people interact with the environment reduce exposure to microorganisms and this may affect the mechanisms of development of immunologic tolerance [29]. For example, consumption by mothers and infants of untreated cow's milk is negatively associated with asthma and

allergies in children regardless of whether they live on a farm [30]. A diverse intestinal flora in early life is associated with reduced risk of allergy at five years of age [31].

The association of gram-negative Gamma *proteobacteria* such as Acinetobacter with atopic disease is supported by the positive correlation of the levels of a regulator of immune tolerance, IL-10, with the abundance of *Acinetobacter* on the skin of healthy but not atopic adolescents [32].

Evidence supporting the microflora hypothesis includes the increased incidence of asthma and allergies in industrialized countries during the last 50 years [33]. This may explain why diseases such as asthma and allergy develop at any age. The major relationship and correlation are between allergic diseases and antibiotic use, correlation between allergic diseases and altered fecal microbiota, in addition to correlation between allergic diseases and dietary changes [34].

The microbes living in a baby's gut during its first month of life may directly impact the developing immune system, leading to a higher risk of allergies and asthma later in childhood [35].

The team, at the University of British Columbia and the Children's Hospital in Vancouver, compared the microbiome at three months and at one year with asthma risk at the age of three. Children lacking four types of bacteria - *Faecalibacterium*, *Lachnospira, Veillonella, and Rothia* (Flvr) - at three months were at high risk of developing asthma at the age of three, based on wheeze and skin allergy tests [36]. The same effect was not noticed in the microbiome of one-year-olds, suggesting that the first few months of life are crucial [37].

Early and chronic parasitic worm infections of gastrointestinal tract protect against respiratory allergies and, in the case of hookworm infections, also for asthma [38]. There are possible interactions between gut parasites and the microbiota because they both inhabit the same organ. Worm parasites seem to be able to manipulate both innate immunity and adaptive immunity [39]. Helminths strongly induce Th-2 responses and increase IgE levels [40]. It is hypothesized that cross-reactive IgE might help prevent atopic sensitization and the development of allergic diseases in children with helminth infections. Helminths are also master inducers of immune regulatory processes [41, 42].

Infections with *H polygyrus* or exposure to its excretory/secretory antigens (collected from cultures of live adults) could prevent experimentally induced airway allergy [41, 42]. Viral respiratory tract infections are not associated with protection against atopy or asthma. Bronchiolitis induced by RSV or rhinovirus has been consistently associated with increased risk of later asthma in numerous studies [43, 44]. Some recent studies have suggested a putative interplay between viruses and pathogenic bacteria in the noses and upper respiratory tracts of young children [44, 45]. The presence of bacteria in nasopharynx was associated with increased respiratory symptoms and asthma exacerbations [46, 47]. The nasopharynx is a reservoir for microbes associated with acute respiratory infections (ARIs). Lung inflammation resulting from ARIs during infancy is linked to asthma development, especially during the critical first year of life. The nasopharynx microbiome is determinant for infection spread to the lower airways, severity of accompanying inflammatory symptoms, and risk for future asthma development. Early asymptomatic colonization with *Streptococcus* was a strong asthma predictor, and antibiotic usage disrupted asymptomatic colonization patterns [47, 48].

Bacterial intestinal infections

The gut microbiota metabolizes dietary fibers, resulting in increased circulating short-chain fatty acids [49]. Short-chain fatty acids ultimately induced seeding of the lungs with DCs with an impaired ability to promote Th-2 cell effector function. These results suggest a mechanism whereby diet in association with the intestinal microbiota could have a direct influence on the development of asthma.

Infection by *H pylori*, especially in early childhood, might confer benefits because protective effects of *H pylori* infection against the development of asthma and allergies have been described [50]. Various persistence determinants of *H pylori* have been shown to be critically important to these protective effects and are being evaluated for further therapeutic applications [51, 52].

A recent study showed that farm dust reduced the production of innate type Th- 2 cytokines by epithelial cells [53]. Maternal exposure to microorganisms can reduce the risk of offspring having allergic diseases. Epigenetic changes after farm exposure might be responsible for increasing the number and function of cord blood T regulatory cells [54].

Lungs support a complex microbiota originating from inhaled microbes and flora from the digestive system [55]. Low microbial diversity in the lung has been found in patients with diseases such as asthma. New studies have linked the composition of the lung microbiome to therapy responses to corticosteroids by uncovering a difference in microbiota composition in steroid-responsive and steroid-resistant patients [56].

Probiotics are defined as viable microorganisms that enhance the host's health [57]. There is great uncertainty about the efficacy of probiotics for preventing and treating asthma and allergies! A meta-analysis of 25 studies that assessed the ef-

fects of probiotic administration in children on atopy and asthma found that administration of probiotics reduces IgE levels and the risk of atopic sensitization but not the risk of asthma or wheezing [58]. The decrease in total IgE was more pronounced when probiotics were administered for longer time, and the reduced risk of allergic sensitization may therefore depend on the specific bacterial strains.

The administration of probiotics during pregnancy and to infants may contribute to the prevention of atopic (eczema) diseases in high-risk infants [58] but not asthma. Probiotics may have great potential for preventing and treating allergies, although the bacterial species, their numbers, and the duration and timing of treatment that are safe and effective are unknown yet [30]. The results of a controlled clinical trial of newborns indicate that 6 months of treatment with oral probiotics protects against IgE-associated dermatitis at 2 years, but only for those at high risk of eczema. The effect disappears after 5 years of age [59].

The future outlook is to continue to focus on the functional and ecologic characteristics of the gut and lung microbiomes of healthy people as well as the features of the lung and gut microbiomes of patients with specific diseases. The development of strategies to improve microbiome colonization patterns will likely enhance health throughout an individual's life. It will be necessary to determine if variations in the microbiome are the cause or effect of allergies and asthma, and longitudinal studies are essential to control for different confounding factors [29]. Microbiome could be used to improve diagnostics as well as treatment and prevention strategies that might include probiotics as well as dietary and lifestyle interventions.

CONCLUSION

The Microbiome can be defined as all microorganisms that inhabit humans and interact with the environment. Microbiome of humans is continuously exposed to many factors such as the use of antibiotics, diet, and infections which may change its diversity and composition and lead to increasing susceptibility to asthma and allergies.

There are differences between the lung and the gut microbiomes of healthy people was well as those with asthma and allergies. The ultimate goal is to understand whether the microbiome is linked to disease and whether manipulation of the microbiome will be useful to preserve lung function, prevent, and treat allergies.

Regulating the microbiome of the mother prenatal and the newborn postnatal seems to be the most promising approach in preventing or ameliorating atopy. Identification of populations at risk is of utmost importance to ensure primary prevention. Effective anti-viral therapies, targeting pathogenic bacteria within the nasopharyngeal microbiome during the first year, could represent a prophylactic approach to asthma [48]. Increasing knowledge of the immunomodulatory effects of microbial-host interactions might also offer a chance to develop novel therapeutic treatments.

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REFERENCES

1. Akdis CA. (2013). Allergy asthma and one health: the size of the problem. GRF 2nd One Health Summit. Swiss Institute of Allergy and Asthma Research (SIAF).
2. Yamauchi K and Inoue H. (2007). Airway Remodeling in Asthma and Irreversible Airflow Limitation-ECM Deposition in Airway and Possible Therapy for Remodeling. Allergol Int. 56(4): 321-329.
3. Boulet LP, FitzGerald JM and Reddel HK (2015). The revised 2014 GINA strategy report: opportunities for change. Curr Opin Pulm Med. 21(1):1-7.
4. Wenzel SE. (2013). Complex phenotypes in asthma: current definitions. Pulm Pharmacol Ther. 26(6): 710-715.
5. Wenzel S, Ford L, Pearlman D, Spector S, et al. (2013). Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med. 368(26): 2455-2466.
6. Bjorksten B, Naaber P, Sepp E and Mikelsaar M. (1999). The intestinal microflora in allergic Estonian and Swedish 2-year-old children. Clin Exp Allergy. 29(3): 342-346.
7. Ursell LK, Metcalf JL, Parfrey LW and Knight R (2012). Defining the human microbiome. Nutr Res. 70(Suppl 1): S38-S44.
8. Kinross JM, Darzi AW and Nicholson JK. (2011). Gut microbiome-host interactions in health and disease. Genome Med. 3:1-11.
9. Arrieta MC, Stiemsma LT, Dimitriu PA, Thorson L, et al. (2015). Early infancy microbial and metabolic alterations affect risk of childhood asthma. Sci Transl Med. 7(307): 307ra152.
10. Ley RE, Peterson DA and Gordon JI. (2006). Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell. 124(4): 837-848.
11. Pennisi E. (2012). Genomics. ENCODE project writes eulogy for junk DNA. Science. 337(6099): 1159.

12. Plotnikoff GA and Riley D. (2014). The human microbiome. Glob Adv Health Med. 3(3): 4-5.
13. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, et al. (2012). Diversity, stability and resilience of the human gut microbiota. Nature. 489(7415): 220-230.
14. Koenig JE, Spor A, Scalfone N, Fricker AD, et al. (2011). Succession of microbial consortia in the developing infant gut microbiome. Proc Natl Acad Sci USA. 108(Suppl 1): 4578-4585.
15. Ivanov II, Atarashi K, Manel N, Brodie EL. et al (2009). Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell. 139(3): 485-498.
16. Basha S, Surendran N and Pichichero M (2014). Immune responses in neonates. Expert Rev Clin Immunol. 10(9): 1171-1184.
17. McLoughlin RM and Mills KH. (2011). Influence of gastrointestinal commensal bacteria on the immune responses that mediate allergy and asthma. J Allergy Clin Immunol. 127(5): 1097-107.
18. Houghteling PD and Walker WA. (2015). Why is initial bacterial colonization of the intestine important to infants' and children's health? J Pediatr Gastroenterol Nut. 60(3): 294-307.
19. Penders J, Gerhold K, Stobberingh EE, Thijs C, et al. (2013). Establishment of the intestinal microbiota and its role for atopic dermatitis in early childhood. J Allergy Clin Immunol. 132(3): 601-607 e8.
20. Van Nimwegen FA, Penders J, Stobberingh EE, Postma DS, et al. (2011). Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. J Allergy Clin Immunol. 128(5): 948-55. e1-3.
21. Ngoc PL, Gold DR, Tzianabos AO, Weiss ST, et al. (2005). Cytokines, allergy, and asthma. Curr Opin Allergy Clin Immunol. 5(2): 161-186.
22. McLoughlin RM and Mills KH. (2011). Influence of gastrointestinal commensal bacteria on the immune responses that mediate allergy and asthma. J Allergy Clin Immunol. 127(5): 1097-1107.
23. Kotecha SJ, Gallacher DJ and Kotecha S. (2016). The respiratory consequences of early-term birth and delivery by caesarean sections. Paediatr Respir Rev. 19:49-55.
24. Hilti M, Burke C, Pedro H, Paul Cardenas, et al. (2010). Disordered microbial communities in asthmatic airways. PLoS One. 5(1): e8578.
25. Huang YJ, Nelson CE, Brodie EL, Desantis TZ, et al. (2011). Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma. J Allergy Clin Immunol. 127(2): 372-81. e1-3.
26. Slater M, Rivett DW, Williams L, Martin M, et al. (2014). The impact of azithromycin therapy on the airway microbiota in asthma. Thorax. 69(7): 673-674.
27. McLoughlin RM and Mills KH. (2011). Influence of gastrointestinal commensal bacteria on the immune responses that mediate allergy and asthma. J Allergy Clin Immunol. 127(5): 1097-1107.
28. Noverr MC and Huffnagle GB. (2005). The 'microflora hypothesis' of allergic diseases. Clin Exp allergy J Br Soc Allergy Clin Immunol. 35(12):1511-1520.
29. Riiser A. (2015). The human microbiome, asthma, and allergy**.** Allergy Asthma Clin Immunol. 11: 35.
30. Haahtela T, Holgate S, Pawankar R, Benjaponpitak S, et al. (2013). The biodiversity hypothesis and allergic disease: world allergy organization position statement. World Allergy Org J. 6(1): 3.
31. Bisgaard H, Li N, Bonnelykke K, Chawes BL, et al. (2011). Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. J Allergy Clin Immunol. 128(3): 646-652.
32. Hanski I, von Hertzen L, Fyhrquist N, Koskinen K, et al. (2012). Environmental biodiversity, human microbiota, and allergy are interrelated. Proc Natl Acad Sci USA. 109(21): 8334-8339.
33. Pawankar R, Baena-Cagnani CE, Bousquet J, Canonica G W, et al. (2008). State of world allergy report 2008: allergy and chronic respiratory diseases.World Allergy Org J. 1(6 Suppl): S4-17.
34. Julia V, Macia L and Dombrowicz D. (2015). The impact of diet on asthma and allergic diseases. Nat Rev Immunol. 15(5): 308-322.
35. Fujimura KE, Sitarik AR, Havstad S, Lin DL, et al. (2016). Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. Nature Med. 22(10): 1187-1191.
36. Williams S. (2015). Gut bacteria could predict asthma in kids. Biology, Health.
37. Ghallagher J. (2015). Good bacteria key to stopping asthma.
38. Leonardi-Bee J, Pritchard D and Britton J (2006). Parasites in Asthma Collaboration. Asthma and current intestinal parasite infection: systematic review and meta-analysis. Am J Respir Crit Care Med. 174(5): 514-23.
39. Maizels R and Yazdanbakhsh M. (2008). T-cell regulation in helminth parasite infections: implications for inflammatory diseases. T Cell Regulation in Allergy. Asthma and

Atopic Skin Diseases. 94: 112-123.

40. Yazdanbakhsh M, Kremsner PG and Van Ree R (2002). Allergy, parasites, and the hygiene hypothesis. Science. 296(5567): 490-494.

41. McSorley HJ and Maizels RM. (2012). Helminth infections and host immune regulation. Clin Microbiol Revs. 25(4): 585-608.

42. Wilson MS, Taylor MD, Balic A, Finney CA, et al. (2005). Suppression of allergic airway inflammation by helminth-induced regulatory T cells. J Exp Med. 202(9): 1199-1212.

43. Feldman AS, Hartert TV, Gebretsadik T, Carroll KN, et al. (2015). Respiratory severity score separates upper versus lower respiratory tract infections and predicts measures of disease severity. Pediatr Allergy Immunol Pulmonol. 28(2): 117-120.

44. Jartti T and Korppi M. (2011). Rhinovirus-induced bronchiolitis and asthma development. Pediatr Allergy Immunol. 22(4): 350-355.

45. Van den Bergh MR, Biesbroek G, Rossen JW, Astrid ATM. Bosch, et al (2012). Associations between pathogens in the upper respiratory tract of young children: interplay between viruses and bacteria. PloS One. 7(10): e47711.

46. Skevaki CL, Tsialta P, Trochoutsou AI, Logotheti I, et al. (2015). Associations between viral and bacterial potential pathogens in the nasopharynx of children with and without respiratory symptoms. Pediatr Infect Dis J. 34(12): 1296-1301.

47. Kloepfer KM, Lee WM, Pappas TE, Kang TJ, et al. (2014). Detection of pathogenic bacteria during rhinovirus infection is associated with increased respiratory symptoms and asthma exacerbations. J Allergy Clin Immunol. 133(5): 1301-1307.

48. Teo SM, Mok D, Pham K, Kusel M, et al. (2015). The infant nasopharyngeal microbiome impacts severity of lower respiratory infection and risk of asthma development. Cell Host Microbe. 17(5): 704-715.

49. Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, et al. (2014). Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nat Med. 20(2): 159-166.

50. Amberbir A, Medhin G, Erku W, Alem A, et al. (2011). Effects of Helicobacter pylori, geohelminth infection and selected commensal bacteria on the risk of allergic disease and sensitization in 3-year-old Ethiopian children. Clin Exp Allergy. 41(10): 1422-1430.

51. Oertli M, Noben M, Engler DB, Semper RP, et al. (2013). Helicobacter pylori γ-glutamyl transpeptidase and vacuolating cytotoxin promote gastric persistence and immune tolerance. Proc Natl Acad Sci. 110(8): 3047-3052.

52. Koch KN, Hartung ML, Urban S, Kyburz A, et al. (2015). Helicobacter urease–induced activation of the TLR2/NLRP3/IL-18 axis protects against asthma. J Clin Invest. 125(8): 3297-3302.

53. Schuijs MJ, Willart MA, Vergote K, Gras D, et al. (2015). Farm dust and endotoxin protect against allergy through A20 induction in lung epithelial cells. Science. 349(6252): 1106-1110.

54. Schaub B, Liu J, Höppler S, Schleich I, et al. (2009). Maternal farm exposure modulates neonatal immune mechanisms through regulatory T cells. J Allergy Clin Immunol. 123(4): 774-782.

55. Marsland BJ, Yadava K and Nicod LP. (2013). The airway microbiome and disease. CHEST. 144(2): 632-637.

56. Goleva E, Jackson LP, Harris JK, Robertson CE, et al. (2013). The effects of airway microbiome on corticosteroid responsiveness in asthma. Am J Respir Crit Care Med. 188(10): 1193-1201.

57. Sanders ME. (2008). Probiotics: definition, sources, selection, and uses. Clin Infect Dis. 46(Suppl 2): S58-61.

58. Elazab N, Mendy A, Gasana J, Vieira ER, et al. (2013). Probiotic administration in early life, atopy, and asthma: a meta-analysis of clinical trials. Pediatrics. 132(3): e666-76.

59. Kuitunen M, Kukkonen K, Juntunen-Backman K, Korpela R, et al. (2009). Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. J Allergy Clin Immunol. 123(2): 335-341.