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Gut microbiota, probiotics, and vitamin D: Interrelated exposures influencing allergy, asthma, and obesity?

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Current evidence supports a role for gut colonization in promoting and maintaining a balanced immune response in early life. An altered or less diverse gut microbiota composition has been associated with atopic diseases, obesity, or both. Moreover, certain gut microbial strains have been shown to inhibit or attenuate immune responses associated with chronic inflammation in experimental models. However, there has been no fully adequate longitudinal study of the relation between the neonatal gut microbiota and the development of allergic diseases (eg, atopic asthma) and obesity. The emergence of promising experimental studies has led to several clinical trials of probiotics (live bacteria given orally that allow for intestinal colonization) in human subjects. Probiotic trials thus far have failed to show a consistent preventive or therapeutic effect on asthma or obesity. Previous trials of probiotics have been limited by small sample size, short duration of follow-up, or lack of state-of-the art analyses of the gut microbiota. Finally, there is emerging evidence that the vitamin D pathway might be important in gut homeostasis and in signaling between the microbiota and the host. Given the complexity of the gut micriobiota, additional research is needed before we can confidently establish whether its manipulation in early life can prevent or treat asthma, obesity, or both. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: *Microbiota, asthma, obesity, allergic, eczema, vitamin D, probiotics, cytokines*

Asthma and obesity are 2 major public health problems in industrialized nations, such as the United States.[1-3] Both diseases are characterized by a state of chronic inflammation and have been associated in multiple studies of children and adults.[4-10] Potential explanations for the link between obesity and asthma include pleiotropic genetic effects,[5,11,12] altered lung mechanics,[13] resistance to treatment with inhaled corticosteroids,[14-16] diet and vitamin D deficiency,[17-21] coexisting morbidity (eg, gastroesophageal reflux), and reduced or altered microbial exposure in early life (see below).

Abbreviations used
Treg: Regulatory T
VDR: Vitamin D receptor

The largest and earliest source of microbial exposure in human subjects comes from the intestinal tract. The gut contains a large and diverse population of microbes that is, quantitatively, the most important postnatal source of microbial stimulation of the immune system.[22,23] The initial gut composition can significantly influence immune system development.[24] Hence disruption of this process early on in life at a time of dynamic changes[25,26] in the infant's gut might have long-term health effects. Both asthma[27] and obesity[28-30] often begin in early childhood, when the gut microbiota is primarily developed. Recent studies in animal models and in human subjects have found a relation among gut microbiota, atopic diseases (eczema, allergic rhinitis, and asthma) (Table I),[31-38] and obesity.[39-43] Early-life factors (ie, diet, medications, hygiene, antioxidants, and nutrients) associated with asthma, obesity, or both[6] might alter the gut milieu. Vitamin D deficiency is widespread worldwide[44] and has been associated with early-life wheeze, reduced asthma control,[20,21,45] and increased body mass index.[46-48] Vitamin D has immune-modulatory properties capable of inhibiting inflammation and infections[49-51] and thus might be important in shaping the early gut microbiota. In this article we first review recent advances in our understanding of the development and immune-modulatory properties of the gut microbiota. Next we discuss current evidence to support a link among the gut microbiota, atopic diseases (including asthma), and obesity. Then we review the outcomes of recent probiotic trials on asthma and obesity. Finally, we review the potential link between vitamin D, asthma, obesity, and the gut microbiota.

GUT MICROBIOTA DEVELOPMENT

Anaerobes (particularly gram-positive Firmicutes and Actinobacteria and gram-negative Bacteroidetes) are the predominant bacteria in the gastrointestinal tracts of adult subjects.[52] In human subjects the gastrointestinal tract is sterile at birth. Multiple

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TABLE I. Studies of the association between the infant's intestinal or intrauterine microflora and asthma-related phenotypes in childhood

Reference	Study type; study area	Sample size	Intestinal microflora measurement	Outcome
Bjorksten et al,[32] 1999	Cross-sectional; Estonia and Sweden	Sixty-two 2-year-old children	Bacterial culture	Allergic children are less often colonized with lactobacilli and anaerobes and more often colonized with aerobes: coliform bacteria and *Staphylococcus aureus*.
Bottcher et al,[33] 2000	Cross-sectional; Sweden	Twenty-five allergic and 47 nonallergic 13-month-old infants	Gas chromatography of bacterial fatty acids	Fatty acid profiles differed between allergic and nonallergic infants. Allergic infants had higher levels of i-caproic acid (associated with *Clostridium difficile*).
Kalliomaki et al,[38] 2001	Longitudinal; Finland	Seventy-six infants	GLC of bacterial fatty acids; FISH of bacterial cells at 3 wk and 3 mo	Fatty acid profiles differed between allergic and nonallergic infants. By using FISH, children with allergic sensitization at 12 mo had more clostridia in infancy.
Penders et al,[35] 2007	Longitudinal (KOALA); The Netherlands	Nine hundred fifty-seven children	RT-PCR of feces at 1 mo	Presence of *Escherichia coli* was associated with increased risk of eczema. *Clostridium difficile* was associated with increased risk of eczema and allergic sensitization at 2 y of age.
Murray et al,[34] 2005	Case-control; United Kingdom	Thirty-three case-control pairs: sensitized wheezy cases vs nonsensitized nonwheezy control subjects (mean age, 4.4 y)	PCR combined with DGGE and quantification of bifidobacteria by means of FISH	There was no difference in prevalence of lactic acid bacteria or bifidobacteria between cases and control subjects. Cases with eczema had fewer bifidobacteria.
Verhulst et al,[37] 2008	Longitudinal; Belgium	One hundred fifty-four children	Bacterial culture at 3 wk of age	Increasing total concentration of anaerobic bacteria was associated with increased odds of wheezing. Increasing concentrations of *Clostridium* species was protective of wheezing in the first year of life.
Forno et al,[108] 2008	Case-control nested within longitudinal study; United States	Twenty-one infants: with vs without eczema	DGGE of stool at 1 and 4 mo	Increase in diversity of gut microbiota was significant in control subjects but not in cases.
Keski-Nisula et al,[129] 2009	Longitudinal; Finland	Four hundred sixty children	Microbial culture of amniotic fluid at time of cesarean section	Intrauterine growth of anaerobic bacteria and *Streptococcus* species was associated with increased risk of doctor-diagnosed asthma at age 15-17 y.

DGGE, Denaturing Gradient Gel Electrophoresis; *FISH*, fluorescence *in situ* hybridization; *GLC*, gas-liquid chromatography.

factors determine gut colonization, including bacterial characteristics, mucosal cell characteristics, mode of delivery, and type of diet.[36,53,54]

The initial neonatal gut colonization is determined either by maternal flora or bacteria from the immediate environment (ie, hospital and health care workers), depending on the mode of delivery.[53,55] The correlation between the maternal vaginal and intestinal flora might ultimately explain the correlation between the maternal and neonatal intestinal flora in children born by means of vaginal delivery.[56-59] Neonates born by means of vaginal delivery are exposed to the mother's vaginal and intestinal flora as they pass through the birth canal and typically harbor communities of bacteria that resemble those of the mother's flora.[55,60] Compared with vaginal delivery, cesarean section is associated with early gut colonization with *Klebsiella* species, *Clostridium* species, and Enterobacteriaceae other than *Escherichia coli*.[36,55]

On the other hand, children born by means of cesarean section are colonized later and less frequently by *Bacteroides* species,[36,53,55] *Bifidobacterium* species,[36,53,55] and *E coli*.[36,53]

Data in mice have shown differences in innate immune responses between pups delivered by means of cesarean section and those born by means of vaginal delivery.[61] Activation of intestinal epithelial cells occurred only in pups born by means of vaginal delivery. This intestinal epithelial cell activation occurs through contact with exogenous endotoxin acquired from maternal body fluids during vaginal delivery.[61] In human subjects, birth by means of cesarean section results in alterations in the composition of the infant's gut flora lasting up to at least 6 months of age.[62] Risk for atopy, asthma, and allergic rhinitis[63-66] has been associated with cesarean section delivery, perhaps because of a lack of exposure to the maternal vaginal flora, gut flora, or both during normal delivery.

The type of feeding instituted early in life also influences neonatal gut colonization.[23,36] Although the data have been somewhat contradictory, in general the numbers of *Clostridium* (especially *C difficile*) species, *Bacteroides* species, enterococcocci, and Enterobacteriaceae (especially *Klebsiella and Enterobacter* species) tend to be lower and the number of staphylococci tend to be higher in breast-fed compared with formula-fed infants, perhaps because of higher exposure to maternal skin flora.[67] One study demonstrated that in breast-fed infants the predominant bacterial species at age 8 weeks was *Bifidobacterium*, whereas in formula-fed neonates *Bacteroides* species predominated.[68]

In a study by Penders et al,[55] hospitalization and premature birth were also associated with a high prevalence of C *difficile* counts similar to those seen after cesarean delivery, which might be related to hospital environmental exposure.[55] In the same study antibiotic use in the first month of life was associated with reduced numbers of anaerobes, such as bifidobacteria and *Bacteroides* species.[55] Similarly, other studies have also found reduced numbers of anaerobes and higher numbers of enterococci, Enterobacteriaceae, and coagulase-negative staphylococci in infants from the neonatal intensive care units, where antibiotics are frequently used.[69,70] Antibiotic use in early life might lead to alterations in gut microbiota and, ultimately, abnormal development of the immune system.[71] However, it has been observed that a majority of bacterial species return to pretreatment levels relatively quickly after an antibiotic course, with the exception of a few species that fail to recover after an extended period of time.[72,73] Although the effect of antibiotic treatment might have long-term effects, no causal association between postnatal antibiotic use and atopic diseases has been demonstrated.[74-78] The association between early antibiotic use and later development of asthma[79] is likely due to reverse causation (ie, antibiotics are more often prescribed to children predisposed to asthma).[37,74,80,81] Limited evidence suggests that antibiotic use during pregnancy[82] and at the time of delivery[83] increases the risk of atopy[82] and persistent wheeze[83] in childhood. However, in the study by Penders et al,[55] maternal antibiotic use in the last month of pregnancy was not associated with changes in the infant's gut microbiota.

Although bacterial colonization of the gut is completed approximately 1 week after birth, the numbers and species of bacteria fluctuate markedly during the first few months of life.[25,26,84] Given the relative instability[25,26] of the intestinal colonization process during early life, any disturbance of this process might affect the microbiota and its function, potentially affecting the host's health.

GUT MICROBIOTA AND IMMUNE RESPONSES

Murine models suggest that bacterial gut colonization is essential for postnatal maturation of T_H1 immune responses and induction of oral tolerance.[85] However, the specific microbes or groups of microbes responsible for this phenomenon have not been confidently identified. In neonatal mice the administration of antibiotics leads to alterations of the intestinal flora and impaired T_H1 immune responses[86] that can be reversed by administration of *Enterococcus faecalis* (and, to a lesser extent, *Lactobacillus acidophilus*) to neonates but not older mice.[87] In another study a full intestinal flora, but not monocolonization with *E coli* or lactobacilli, supported normal oral tolerance.[88] In germ-free mice presentation of a bacterial capsular polysaccharide A of *Bacteroides fragilis* by intestinal dendritic cells activates $CD4^+$ T cells, elicits appropriate cytokine production, and restores adequate balance of T_H1/T_H2 immune responses. In rodents some *Lactobacillus* species strains have been shown to induce production of IL-12 and IFN-γ and suppress production of total IgE.[89-91] Neonatal treatment with *Lactobacillus rhamnosus* GG has been shown to inhibit the development of experimental asthma in mice that was associated with increased forkhead box protein 3 expression and TGF-β production.[92] In another study oral treatment with live *Lactobacillus reuteri* (but not *Lactobacillus salivarius*) significantly attenuated inflammatory cell influx to the lung and decreased allergen-induced airway hyperresponsiveness in mice.[93] In a follow-up study Karimi et al[94] demonstrated that the *L reuteri*-induced attenuation of allergic airway response was mediated through the suppressive function of regulatory T (Treg) cells. In other murine models stimulation with LPS increases proliferation and efficiency of Treg cells through activation of their Toll-like receptors.[95,96] *In vitro* experiments show that cultured human intestinal cells produce TGF-β in response to stimulation with microbial antigens[97] and that some bifidobacterial species stimulate production of IL-10 in cord blood.[98]

Experimental data contributing to understanding of the gut microbiota's effects on immune modulation are reviewed in detail in this issue by McLoughlin and Mills.[99] Collectively, these data suggest complex effects of gut microbiota on adaptive, innate, and Treg immunity that could influence asthma and obesity.

GUT MICROBIOTA AND ATOPIC DISEASES

In cross-sectional studies the composition of the gut flora differs between atopic and nonatopic infants.[31,32] In studies from Estonia and Sweden, atopic infants have lower counts of lactobacilli, bifidobacteria, and *Bacteroides* species and higher levels of i-caproic acid (a marker of *C difficile*) compared with nonatopic infants.[32,33] Although an English study found no differences in bifidobacteria or lactic acid bacteria between children (ages 3-5 years) with and without atopic wheeze, it had a small sample size (n = 66) and no additional data on stool cultures.[34] Although most cross-sectional studies have examined only atopic dermatitis as an outcome, one study found increased risk of asthma with increased *C difficile* colonization.[35]

Few prospective studies have examined the relation between the gut flora in early life and atopy. Among 76 Finnish children, bacterial cellular fatty acid profile and a reduced ratio of bifidobacteria to clostridia (determined by means of fluorescence *in situ* hybridization) in stool samples at age 3 weeks was associated with allergen sensitization at age 1 year.[38] In a study of 324 European infants followed from birth to age 18 months, neither

time to gut colonization with 11 bacterial groups nor the ratio of strict anaerobic to facultative anaerobic bacteria in cultures from neonatal stool samples was associated with eczema or food allergy.[36] In contrast, a study of 957 Dutch infants showed that the presence of *C difficile* in stool samples at age 1 month (assessed by means of quantitative real-time PCR) was associated with increased risk of atopic dermatitis, recurrent wheeze, and allergic sensitization at age 2 years.[35] In that study early colonization with *E coli* was associated with parental report of eczema but not with objectively diagnosed atopic dermatitis. In a Belgian study wheezing in the first year of life was associated with an increased total concentration of anaerobic bacteria and a decreased concentration of *Clostridium* species in stool cultures obtained at 3 weeks of age.[37]

Published longitudinal studies of the neonatal gut flora and atopy or atopic diseases have been limited by inadequate statistical power,[36,38] noncomprehensive microbiologic assessment of neonatal stool samples,[35,36,38] heterogeneity of study participants,[36,38] inadequate data on maternal and neonatal diet,[35,36,38] nonassessment of the maternal gut and vaginal flora,[35,36,38] failure to examine modification of the effect of the gut flora on atopy by mode of delivery,[35,36,38] and nonuse of novel statistical approaches to explore potential microbial interactions.[35,36,38] Moreover, studies that examined the association between neonatal gut flora and wheeze or asthma[35,37] did not examine differences in gut microbiota between atopic and nonatopic wheeze/asthma.

GUT MICROBIOTA AND OBESITY

Experimental models highlight several mechanisms connecting the gut microbiota to obesity and metabolic disorders. The recognition that gut microbiota is important in the regulation of energy extraction from the diet[100] came from the observation that germ-free mice (raised in the absence of microorganisms) were leaner than mice with a normal gut microbiota, even though mice with a normal gut microbiota were fed 30% less calories.[101] Moreover, when germ-free mice were transplanted with gut microbiota harvested from mice with normal gut microbiota they gained 60% body fat and became insulin resistant, despite lower food intake.[101] Subsequent studies also demonstrated the role of gut microbiota in regulating energy storage as triglyceride[101,102] and energy expenditure from fatty acid oxidation.[102]

Most recently, gut microbiota has been linked to low-grade inflammation through activation of innate immunity through the LPS–Toll-like receptor 4 axis.[103] Cani et al[104] demonstrated that mice fed a high-fat diet for 2 to 4 weeks exhibited a significant increase in circulating LPS levels (described as "metabolic endotoxemia") and that these mice became obese and had obesity-associated metabolic disorders.[104,105] Similarly, mice infused with LPS (to reach levels observed in mice that were fed a high-fat diet) also had obesity and obesity-associated metabolic disorders.[104,105]

Obesity has further been shown to be associated with altered gut microbial composition in human subjects[39,43] and mice.[41] The guts of obese human subjects were shown to have reduced numbers of Bacteroidetes and increased numbers of Firmicutes compared with those of their lean counterparts.[39] In a few obese human subjects, an increased proportion of fecal Bacteroidetes was found to parallel weight loss on a hypocaloric diet during a 1-year intervention trial.[39] Compared with lean mice, genetically obese mice (leptin-deficient mice) have reduced numbers of Bacteroidetes and increased numbers of Firmicutes isolated from the distal gut.[41] Diet-induced obesity in animal models also led to increased Mollicutes (a class of Firmicutes) that was reversible with dietary manipulation to limit weight gain.[42] The fact that microbial composition is reversible with dietary modification suggests that differences in the gut composition of the obese and lean phenotypes are related to dietary factors independent of the obese state.[106,107]

Data on gut microbiota and obesity in children are sparse. In a study on probiotics and allergic diseases, Kalliomaki et al[40] demonstrated that children who had normal weight at the age of 7 years had a higher number of *Bifidobacterium* species and lower numbers of *Staphylococcus aureus* in infancy than those who were overweight at age 7 years.

Collectively, current evidence supports a role for gut microbiota in the pathogenesis of diet-induced obesity and its related metabolic disorders, which might be reversible with diet and/or gut microbiota manipulation.

PROBIOTICS, ATOPIC DISEASES, AND OBESITY

Emerging evidence suggests that a less diverse population of intestinal anaerobes in early life is associated with both atopic diseases (Table I) and obesity.[43,108] Probiotics (live bacteria given orally that allow for intestinal colonization) provide a relatively safe microbial stimulus by means of cultures of organisms that are part of the gut flora of healthy infants.[109] In a study of 132 infants with a family history of atopy,[110] treatment with *L rhamnosus* strain GG before and after birth halved the risk of eczema (95% CI for relative risk, 0.3-0.8) but not that of allergen sensitization by age 2 years. These results remained appreciably unchanged after 4[111] and 7[112] years of follow-up. Interestingly, whereas the frequency of atopic sensitization at the age of 7 years was similar between the placebo and probiotic group, allergic rhinitis and asthma tended to be more common in the probiotic group,[112] Administration of lactobacilli GG to atopic children has been associated with increased production of cytokines produced by Treg cells (IL-10 and TGF-β)[113,114] and reduced severity of atopic dermatitis in a small number of infants.[69] Another small clinical trial showed reduced severity of atopic dermatitis in children (aged 6-18 months) with moderate to severe disease by means of administration of *Lactobacillus* fermentum,[115] which might be mediated by increased secretion of IFN-γ by T_H1 cells.[116] In a recent study of 925 mother-infant pairs, prenatal administration of probiotics (containing 4 bacterial strains) during the last month of pregnancy and postnatal administration of probiotics and prebiotics from birth to age 6 months resulted in short-lived changes in the neonatal gut flora and reduced the incidence of atopic eczema (but had no effect on other atopic diseases or allergic sensitization) at age 2 years.[117] In the same clinical trial, among the 891 children with complete follow-up at age 5 years, prenatal and postnatal probiotic supplementation did not prevent eczema, allergic rhinitis, or asthma at the age of 5 years.[118] However, cesarean section–delivered children supplemented with probiotics had fewer IgE-associated allergic diseases, such as eczema, and less allergic sensitization.[118] Probiotics have not been shown to prevent asthma. In one study probiotic administration was associated with increased wheezing in children.[119]

A recent meta-analysis[120] of 12 clinical trials, which included some of the trials presented here, did not find a significant

reduction in the symptoms or severity of eczema in children who were treated with probiotics. As pointed out by the authors, there was significant heterogeneity between studies.[120] Although there is still a potential role for probiotics in preventing childhood atopic dermatitis and other allergic diseases, there are many unanswered questions, including strain, dosing, and timing of probiotic administration and the population or populations most likely to benefit (eg, neonates born by means of caesarean section and formula-fed infants).

Although gut microbiota manipulation in experimental models has shown promising results in controlling obesity, findings from clinical trials in human subjects are conflicting and potentially confounded by dietary habits, antibiotics, nutritional supplementation, and physical activity. Findings from a randomized double-blind controlled trial of prenatal and postnatal administration of *L rhamnosus* (beginning 4 weeks before expected delivery and continuing for 6 months after delivery) suggest that probiotics might modify the growth pattern of the child by restraining the excessive weight gain that occurs in the first 1 to 2 years of life but not that between age 2 to 4 years.[121] Maternal probiotic supplementation of 265 pregnant women in the first trimester did not show significant differences in either prenatal or postnatal growth rates.[121,123]

VITAMIN D, GUT MICROBIOTA, ASTHMA, AND OBESITY

Vitamin D deficiency has been associated with early-life wheeze, reduced asthma control[20,21,45] and allergic diseases,[20,45] and increased body mass index.[46-48] In our recent review in this *Journal*,[6] we had identified both gut microbiota and vitamin D as potential common early-life exposures for asthma and obesity. It is unknown whether vitamin D deficiency affects the composition of the intestinal microbiota. Although a small study suggested that decreased vitamin D intake was correlated with differences in fecal microbiota composition,[124] this needs to be verified in larger cohorts.

Given the role of vitamin D in Treg and dendritic cell development and function (reviewed in Griffin et al[125] and in Adorini and Penna[126]), it is possible that the host's vitamin D status could modify the effect of the intestinal microbiota on the immune system. For example, mice that lack the vitamin D receptor (VDR) have chronic, low-grade inflammation in the gastrointestinal tract.[127] Furthermore, the absence of the VDR leads to decreased homing of T cells to the gut, resulting in further inflammation in response to normally nonpathogenic bacterial flora.[127] Intestinal VDR has also been shown to be directly involved in suppression of bacteria-induced nuclear factor-κB activation.[128] Wu and colleagues[128] also showed that commensal bacterial colonization affects both the distribution and expression of VDR in intestinal epithelial cells, suggesting a dynamic interplay between these bacteria and the receptor.

Thus emerging evidence suggests that the vitamin D pathway is a potentially important modifier of the effects of intestinal flora on inflammatory disorders.

CONCLUSIONS

Significant differences between the gut flora of children in industrialized and developing nations suggest that the high prevalence of allergic diseases (eg, atopic asthma) and obesity in affluent nations might be due to changes in the intestinal flora of young infants. Although findings from cross-sectional[31-33] and birth cohort[7,8,16] studies suggest that the maternal and neonatal gut flora influence childhood atopic diseases and obesity, these studies have been limited by small sample size,[38] inadequate assessment of the composition and determinants (eg, diet) of the neonatal gut flora,[35,38,121-123] and absence of data on the maternal vaginal or gut flora.[35,38,121-122]

Probiotic supplementation with specific strains of microbes might be beneficial in the prevention of childhood atopic dermatitis when given in the prenatal or early postnatal life. However, the results of several trials have been inconsistent with regard to the type of probiotic used, the dosing and timing of the agent selected, and the population or populations likely to benefit. On the basis of current data, we cannot yet recommend probiotics as preventive treatment for atopic dermatitis, allergic sensitization, asthma, or obesity.

Recent experimental and epidemiologic data suggest diverse gut colonization early in life, rather than a specific microbial strain or strains, is likely the key factor in promoting normal immune development and maintaining immune homeostasis. Additionally, the role of the VDR and the host's vitamin D status have not been accounted for in these studies. Therefore well-designed birth cohort studies with extensive data on neonatal gut and maternal vaginal/gut microbiome, immune responses, vitamin D status and vitamin D genomics, and confounding/modifying variables (eg, maternal and neonatal diet) are needed to further delineate the underlying immune modulation by gut microbiota important in the development and prevention of allergic diseases, asthma, and obesity.

What do we know?

- **Neonatal gut microbial colonization is important in promoting and maintaining a balanced immune response.**
- **Current data suggest that reduced or altered neonatal gut microbiota composition influences childhood atopic dermatitis.**
- **Probiotic supplementation in the prenatal or early postnatal life might be beneficial but cannot be confidently recommended for the prevention of atopic dermatitis.**

What is still unknown?

- **There has been no fully adequate longitudinal study of the early-life gut microbiota and the development of asthma and obesity.**
- **There are no current data to support the use of probiotics in the treatment or prevention of asthma and obesity.**

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