Nutrition, gut microbiota and child health outcomes

Frida Karlsson Videhult and Christina E. West

Purpose of review
Diet is one of the main drivers of the composition and function of the gut microbiota. The scope of this review is to summarize recent studies assessing the role of gut microbiota in clinical pediatric conditions and to review studies using nutritional approaches to favorably modify the gut microbiota to improve health outcomes in children.

Recent findings
New studies underscore that breastfeeding and infant diet impact the gut microbiome and metagenome. A comprehensive study using metagenomic shotgun sequencing, suggests that the cessation of breastfeeding rather than the introduction of solid foods, drives the functional maturation of the infant gut microbiome toward an adult-like state. There is further support for the view that a disturbed early gut microbiota is implicated in allergic and autoimmune diseases. New studies using prebiotics, probiotics, and synbiotics in various pediatric disorders have yielded promising results, yet the evidence for specific guidelines on their use is still low.

Summary
Intestinal dysbiosis is associated with several pediatric disorders but a cause–effect relationship remains to be clearly demonstrated in most conditions. Future studies using new systems biology approaches are anticipated to provide further insight into the functional capacities of the gut microbiome and its establishment in childhood. This may then lay the ground for improved treatment and prevention strategies targeting the gut microbiota.

Keywords
breastfeeding, dysbiosis, introduction, pediatric, prebiotics, probiotics

INTRODUCTION

A growing body of evidence implicates disturbed intestinal colonization and reduced microbial diversity to be associated with the global increase in noncommunicable diseases (NCDs) [1]. NCDs affecting children and adolescents include obesity with its related comorbidities, autoimmune diseases, allergic diseases and asthma. Dietary change has also been implicated in the pathogenesis of NCDs [2] and as diet is one of the main drivers of the composition and functions of the gut microbiota [3], this has led to interest in dietary interventions to promote a healthy gut microbiota and ultimately, to promote health. Strategies used to date include dietary interventions and the administration of pre and probiotics or their combination (synbiotics). Both pre and probiotics have been added to infant foods and there is also increasing interest in their possible role in the treatment of common pediatric conditions such as colic and constipation. The scope of this review is to summarize recent findings from clinical studies assessing the impact of nutrition and gut microbiota on child health outcomes.

STUDIES IN INFANCY: NEW FINDINGS

Over the last decades, there has been interest in uncovering how the gut microbiota establishment is influenced by early feeding. With the advent of new powerful sequencing techniques, this can now be studied in more detail. Using metagenomic shotgun sequencing, a recent Swedish study of healthy infants reported discontinued breastfeeding rather than the introduction of solid foods, to be the main driver of compositional and functional maturation of the gut microbiome [4▪▪]. Consistent with previous reports, the microbiome of the breastfed infants was abundant in bifidobacteria but also in *Lactobacillus* species that are commonly used as probiotics such as *Lactobacillus casei* (*L. casei*)/*L. paracasei, L. johnsonii/L. gasseri,*

Faculty of Medicine, Department of Clinical Sciences, Pediatrics, Umeå University, Umeå, Sweden

Correspondence to Christina E. West, Department of Clinical Sciences, Pediatrics, Umeå University, SE-901 85 Umeå, Sweden.
E-mail: christina.west@umu.se

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KEY POINTS

- The current collected evidence indicates that intestinal dysbiosis is associated with several pediatric disorders; however, a cause-effect relationship is yet to be decided.
- Cessation of breastfeeding rather than introduction of solid foods appears to drive the functional maturation of the infant gut microbiome.
- Implementation of new systems biology approaches are anticipated for further insight into the functional capacities and establishment of the pediatric gut microbiome. This may then lay the ground for improved treatment and prevention strategies targeting the gut microbiota and thus warrant safe and specific guidelines.

and *Bifidobacterium longum*. A likely explanation for this is that human milk is rich in bioactive factors such as human milk oligosaccharides that act as natural prebiotics, and that human milk may provide the infant gut with beneficial bacteria such as bifidobacterial strains [5]. In the vaginally delivered infants' microbiomes, genes capable of breaking down monosaccharides in breast milk were common; however, the increased capacity to degrade polysaccharides promoted by the introduction of solid foods was not evident until the infants stopped breastfeeding [4▪▪]. Bergström *et al.* [6▪] also reported the cessation of breastfeeding to be the major factor affecting microbial composition up to 12 months of age. As assessed by quantitative polymerase chain reaction (q-PCR), a proxy enterotype based on the relative levels of *Bacteroides* spp. and *Prevotella* ssp. was established between 9 and 36 months of age. Of note, 30% of the infants shifted enterotype during this time span. Studies examining the impact of mixed feeding (breast milk plus formula) on the gut microbiome are scarce but in a small longitudinal study using 16S sequencing, exclusively breastfed infants displayed lower species richness and diversity compared with mixed-fed infants [7▪]. After the introduction of solid foods there were marked changes in the gut microbiome, and this was especially evident in the mixed-fed group. Using predictive bioinformatics, they further reported different genetic and metabolic pathways to be activated in exclusively breastfed and mixed-fed infants. Collectively, these studies give further support for the theory that infant feeding impacts the gut microbiome and metagenome with possible long-term programming effects on metabolism.

MICROBIOTA AND METABOLIC PROGRAMMING

In the large prospective Child, Parent and health: Lifestyle and Genetic constitution (acronym in Dutch (KOALA) birth cohort study fecal samples of more than 900 infants were collected ~1 month postpartum and analyzed by q-PCR targeting bifidobacteria, the *Bacteroides fragilis* group, *Clostridium difficile, Escherichia coli,* lactobacilli, and total bacteria counts. There was no association between the early intestinal microbiota composition and subsequent weight development in the whole cohort [8▪▪]. However, in the subgroup of children whose mothers had an alternative lifestyle, that is, vegetarian and/or organic diets, higher counts of *Bacteroides fragilis* were associated with lower BMI z-score.

Probiotic interventions have been suggested to favorably influence the gut microbiota and to induce metabolic benefits [9]. Paradoxically, there have also been concerns about using *Lactobacillus* strains as they belong to the *Firmicutes* phylum [10], which has been associated with obesity [11]. In a recent follow-up study at school age of a probiotic RCT, we found neither benefit nor harm on body composition, growth, metabolic, or inflammatory markers following supplementation with *Lactobacillus paracasei* ssp. *paracasei* F19 during weaning [12▪,13]. Ongoing prospective cohort studies and follow-up studies of probiotic RCTs initiated in early life are anticipated to shed more light on the role of gut microbiota establishment in metabolic programming.

COLIC: PRE, PRO, AND SYNBIOTICS

Infantile colic, regurgitation and obstipation often cause parental distress and lead to pediatric visits. As discussed, breastfed infants have a microbiota generally considered rich in 'beneficial' bacteria such as *Bifidobacterium* and *Lactobacillus* and a growth reduction of gas producing bacteria such as *Clostridium* [4▪▪,6▪]. In randomized controlled trials, treating colicky infants with *L. reuteri* DSM 17938 has led to significant reduction of crying time, regurgitation, and functional constipation compared with placebo [14,15▪]. In contrast, Sung *et al.* [16▪] reported transient reduction in fuss time and longer sleeping duration at 1 month of treatment in the placebo group compared with *L. reuteri* DSM 17938. This increased fussing occurred only in formula-fed and not in breastfed infants. Another recent study evaluated *L. reuteri* DSM 17938 for the prevention of colic with a significant reduction of crying time at 1 and 3 months of age [17▪]. Generally, *L. reuteri* DSM 17938 appears to reduce crying time in

breastfed infants with colic, however, the role of this probiotic in colicky formula-fed infants needs further study. Also for the prevention of colic, the use of *L. reuteri* DSM 17938 appears to be effective but this needs confirmation in other study settings [18].

To promote the growth of 'beneficial' bacteria, specific prebiotics have been added to infant formula and evaluated in clinical trials. In a recent double-blind RCT, intake of galacto-oligosaccharides supplemented formula showed similar trends of *Bifidobacterium* and *Lactobacillus* development as the breastfed reference group, and reduced the risk of colic and regurgitation compared to infants receiving formula without galacto-oligosaccharides [19]. There is also increasing interest in synbiotics to provide both the 'beneficial' bacteria and their substrate. Feeding infants a mixture of seven probiotic strains and fructooligosacharides led to a reduction of crying time more than 50% at day 7 and 30, compared with a control group that was randomized to placebo formula [20]. In another prospective, double-blind RCT assessing the effects of a synbiotic yoghurt drink containing *Streptococcus thermophilus, L. bulgaricus* and *B. animalis* ssp. *lactis* and inulin on illness episodes (diarrhea, upper respiratory infection, and febrile illness) there was a reduction in days of fever compared with placebo [21]. The intervention group tended to have a greater frequency of loose stools and more absence from child care, though the difference was not statistically significant. Collectively, more studies evaluating the effects of prebiotics and synbiotics in these conditions are needed before any firm conclusions can be drawn.

MICROBIOTA, PROBIOTICS, AND ALLERGIC DISEASE

There is also continued interest in the role of dysbiosis in programming of the allergic phenotype. Azad *et al.* [22▪], reported low gut microbiota richness and an elevated *Enterobacteriaceae/Bacteroidetes* ratio in infant stool to be associated with increased risk of subsequent food sensitization in the population-based Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study. They also found food-sensitized infants to have decreased abundance of *Ruminococcaceae* at 1 year. This could be consistent with the findings from a case-control study in infants at high risk of allergic disease where we found a lower relative abundance of *Ruminococcaceae* in stool samples of infants that subsequently developed atopic eczema compared with infants that did not develop any allergic manifestations [23▪]. Of note, a low relative abundance of the genus *Ruminococcus* was also associated with exaggerated inflammatory innate immune responses. Collectively, these findings give further support for the hypothesis that the absence of potentially immunemodulatory bacteria may increase the risk of developing allergic manifestations. As ruminococci are capable of degrading fiber and are part of the 'core' microbiome in adults [24], future studies should examine the significance of this.

In a recent study examining the effects of probiotics on the gut microbiome in cow's milk allergic infants, Berni Canani *et al.* [25▪] reported that an extensively hydrolyzed casein (EHCF) formula with added *L. rhamnosus* GG (LGG) led to the enrichment of specific bacteria that are associated with butyrate production. Butyrate is a known substrate for coloncytes and has been implicated in reinforcing gut integrity (which is recently reviewed elsewhere [26]). Infants treated with EHCF + LGG had a bimodal distribution of butyrate production following 6 months treatment, compared with EHCF alone. Known butyrate producers, *Faecalibacterium*, *Blautia*, *Ruminococcus,* and *Roseburia* were enriched in high butyrate samples whereas *Bacteroides* was significantly reduced. *Blautia* and *Roseburia* were also enriched in children that became tolerant in comparison with those who did not. As speculated by the authors, these species might have led to increased butyrate production and increased gut integrity.

During the year in review there are also two reports from the ProPact RCT. In this RCT, perinatal intake by pregnant mothers of low-fat fermented milk with a probiotic combination reduced the incidence of eczema at 2 and 6 years of age in their children, compared with a sterile placebo milk [27,28]. However, the clinical benefit appears not to be linked to effects on gut microbial diversity at 3 months or at 2 years of age [29▪]. As the probiotic administration was given to the mothers only, an alternative explanation for the benefit might be through influences on breast milk composition [30]. In another follow-up study of a probiotic RCT in infancy, there was no effect on the long-term gut microbiota establishment [31], which is consistent with previous reports. Although recent meta-analyses [32] report that probiotics in pregnancy, during breastfeeding and/or when given to the infant reduce the risk of infant eczema, the evidence is still weak. Consequently, expert bodies have not been able to launch specific guidelines. However, when considering all critical outcomes, the World Allergy Organization now suggests using probiotics for allergy prevention in pregnant and breastfeeding mothers at high risk for having an allergic child, and in infants at high risk of developing allergic disease (based on family history) [33]. In their guidelines they stressed that

the recommendation is conditional and based on low-quality evidence, and that no specific guidance on the most effective strain(s), dosages or initiation and duration of treatment can be given. Hence, more specific guidelines are still requested [18].

GUT MICROBIOTA MODULATION IN IRRITABLE BOWEL SYNDROME, CROHN'S DISEASE, AND CELIAC DISEASE

In a pilot study assessing a low fermentable substrate diet in children with irritable bowel syndrome, the diet was significantly associated with decreased abdominal pain frequency and severity [34]. Children responding to treatment appeared to have a different fecal microbiome compared to non-responders, both at baseline and during the intervention. In a larger, double-blind, randomized, crossover study, the same group studied the efficacy of a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet on both clinical outcomes and gut microbial composition using 16S sequencing in children with irritable bowel syndrome [35▪]. The low FODMAP diet reduced abdominal pain and children responding to the diet had a microbiota with greater saccharolytic capacity. The authors suggest that identifying a microbiota with greater saccharolytic capacity might serve as a biomarker predicting the response to a low FODMAP diet. Changes in the gut microbiota milieu have been proposed to be a mediator of the therapeutic properties of exclusive enteral nutrition in patients with Crohn's disease [36]. Quite surprisingly, the gut microbial diversity, *Faecalibacterium prausnitzii* and butyrate concentrations decreased during the course of exclusive enteral nutrition in children with Crohn's disease compared to healthy controls with no family history of inflammatory bowel disease [36]. This was later reversed to pretreatment levels when the participants resumed their normal diet. Concomitant with this presumed 'unhealthy' microbiota there was paradoxically improved clinical outcomes and reduction in colonic inflammatory markers. However, the relevance of these findings needs to be further elucidated.

In celiac disease, the adherence to a strict gluten-free diet (GFD) is sometimes difficult and patients might still suffer from clinical symptoms and nutritional deficiencies with subsequent continued inflammation and gut microbiota dysbiosis. As specific probiotics have been shown to attenuate inflammation, children newly diagnosed with celiac disease were randomized to intake of *Bifidobacterium longum* CECT 7347 or placebo for 3 months in a double-blind, exploratory trial [37▪]. Regardless of treatment, the adherence to a GFD was positively correlated with growth parameters and the probiotic group displayed increased height compared to the placebo group. Further, probiotic treatment reduced the number of the *B. fragilis* group and secretory IgA. In another RCT assessing the effects of two probiotic *Bifidobacterium breve* strains in children with celiac disease on a GFD, the intervention decreased the production of the anti-inflammatory cytokine TNFα compared with placebo [38]. Collectively, these studies suggest possible benefits of probiotic administration in children with celiac disease, but need further confirmation in larger trials.

DYSBIOSIS AND DIABETES

In a recent report from the Environmental Determinants of Diabetes in the Young (TEDDY) study, which includes children at high risk for type 1 diabetes in Finland, Sweden, Germany, and the USA, great variability in both the composition and diversity of the gut microbiomes among the different geographical sites were seen as assessed by 16S sequencing [39▪▪]. Even in this population of homogenous human leukocyte antigen (HLA) class II genotype and thereby similar genetic risk, there were marked differences according to geographical region. The underlying reason for these variabilities is unknown as the differences remained even after adjusting for early-life and dietary variables. In the same prospective cohort study, the effect of early probiotic exposure and dietary soluble fiber (that may influence gut microbiota composition and shape the immune response) were also examined in relation to islet autoimmunity. Probiotic exposure ($\leq$27 days of life) was associated with reduced risk of islet autoimmunity compared with later supplementation or no probiotics [40▪▪]. Conversely, intake of dietary soluble fiber in early childhood was not associated with islet autoimmunity or type I diabetes [41]. Future studies need to examine the significance of these findings.

CONCLUSION

There is continued interest in the role of intestinal dysbiosis in a large number of conditions affecting the pediatric population. However, a clear cause-effect relationship remains to be demonstrated in most conditions. Powerful new systems biology approaches will enable studies that can provide further insight into the functional capacities of the gut microbiome and its establishment in childhood. This may then lead to improved treatment and prevention strategies targeting the gut

microbiota, and may also underlie safe and specific guidelines.

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Conflicts of interest

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- ■ of special interest
- ■■ of outstanding interest

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In this large observational cohort study, including 330 infants' significant changes in the gut microbiota occurred after the cessation of breastfeeding. Positive correlations were seen between increases in BMI, the *Clostridium leptum* group and *Eubacterium hallii* between 9 and 18 months of age indicating that these butyrate-producing groups might contribute to an increased energy harvest. A bimodal distribution of the *Prevotella/Bacteroides* ratio was reported between 18 and 36 months of age.

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The introduction of solid foods introduces the infant gut microbiota to novel bacterial species not supported by breast milk and/or formula. This study suggests that breast milk eases the transition into solid foods by providing the gut microbiome with a greater plasticity.

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In this clinical follow-up study, intake of the probiotic *Lactobacillus paracasei* ssp. *paracasei* F19 during weaning had no impact on body composition or metabolic biomarkers, compared with placebo. Collectively, this suggests neither beneficial nor harmful effects on metabolic programming by this probiotic when given in infancy.

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