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CHILD HEALTH AND THE GUT MICROBIOME

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Abstract: In this review, we summarized the most important, accessible, and relevant literature published between April 2019 and March 2020 on the gut microbiota in child health. The first part of the review focuses on literature describing changes in microbiota composition in a wide spectrum of pathologies, while the subsequent section focuses on the impact of antimicrobial treatment and nutritional intervention on the pediatric microbiota during early infancy and development.

Keywords: Pediatric population, Nutrition, Dysbiosis, Development, Antibiotics.

GUT DISBIOSIS IN THE PEDIATRIC POPULATION

Disturbances in microbial homeostasis (or dysbiosis) have been implicated in the pathogenesis of several pathologies. Sixteen research papers relating to gastrointestinal diseases, autoimmune diseases, acute lymphocytic leukemia, infectious diseases, neurologic and cardiac disorders in children were identified.

Gastrointestinal and autoimmune diseases

Inflammatory bowel diseases (IBD) are the exemplar medical conditions of the microbiome era in which disturbances in microbial populations were first described and associated to disease pathogenesis. Sila et al[1] analysed the intestinal microbiota in newly diagnosed pediatric IBD patients and compared it to the patients' healthy siblings with same genetic and environmental background and to healthy unrelated controls. Microbial diversity differed significantly between IBD patients, healthy siblings and unrelated controls. In the pediatric IBD cohort, the genera *Eubacterium*, *Lactobacillus*, *Enterobacter* and *Clostridium* were significantly reduced whereas *Streptococcus*, *Prevotella* and *Escherichia* were abundantly present[1]. Anti-*Saccharomyces cerevisiae* antibody (ASCA) is associated with the diagnosis of Crohn's disease (CD) and may reflect a loss of tolerance to yeast, possibly exacerbated by the presence of an inflamed more permeable gut wall. ASCA is highly predictive but poorly sensitive for CD diagnosis[2]. Kansal et al[2] explored the association between ASCA and the gut microbiota in children with CD and unveiled that ASCA-positive and ASCA-negative CD patients have significant different gut microbial composition, which could possibly influence the phenotype of the disease. Obesity has been associated with a wide spectrum of liver abnormalities. Zhao et al[3] investigated the intestinal microbiota in obese children with nonalcoholic fatty liver disease (NAFLD). Deep sequencing of gut microbiota in stool samples revealed large differences

in gut microbiota between obese children with and without NAFLD compared to healthy controls which reflected in several metabolic pathways differentially enriched among these groups. Interestingly, *Faecalibacterium prausnitzii* was the only species that discriminated between obese children with and without NAFLD[3]. Another study further confirmed the lower proportion of *Bacteroidetes* in obese children. At the genus level, *Faecalibacterium*, *Phascolarctobacterium*, *Lachnospira*, *Megamomas* and *Haemophilus* were more abundant in the obese group compared to the normal weight group whereas *Oscillospira* and *Dialister* were significantly reduced. The authors also highlighted that gut microbial diversity decreased with increasing body weight, further underlining the role of gut dysbiosis in the development of obesity in children[4]. In recent years, the impact of *Helicobacter pylori* infection on the gut microbiota has also gained more attention. Miao et al[5] explored this relationship in the pediatric population by examining gastric mucosal biopsies from children with gastrointestinal symptoms. As similar for the adult population, *H. pylori*-positive children were mainly dominated by the genus *Helicobacter*. They also concluded that the characteristics of the gastric microbiota were mainly affected by *H. pylori* infection rather than the disease state (i.e., gastric ulcers) itself[5]. The function and composition of the gut microbial community have also been associated with the risk of autoimmune diseases, including type 1 diabetes. Paun et al[6] investigated whether immune responses to gut microbiota are associated with autoreactivity to host tissue outside the gut. Their analysis revealed associations between antibody responses to intestinal bacteria and diagnosis of type 1 diabetes. Furthermore, they presented a platform to investigate antibacterial antibodies in biological fluids useful to study therapeutic interventions in autoimmune diseases[6].

Acute lymphocytic leukemia

Haematological malignancies are the most common type of pediatric cancers, with acute lymphocytic leukemia (ALL) the most frequently occurring during childhood. Haematopoietic stem cell transplantation (HSCT) is employed as curative immunotherapy. This procedure can be accompanied by severe side effects, such as bloodstream infections, acute graft-versus-host disease (aGvHD) and death. The gastrointestinal tract is the predicted reservoir for most bloodstream infections after HSCT[7]. Three research papers investigated the microbial signature associated with side effects related to HSCT[8-11]. Kelly et al[8] studied which bacteria where associated with bloodstream infections in ALL patients undergoing HSCT and whether these species originated from the gut. They showed that bloodstream infections were mainly caused by *Escherichia coli* and *Enterococcus faecium* which also dominated the gut prior to occurrence of the infection[8]. Another research performed a longitudinal study of immunological markers and microbial composition in relation to clinical outcomes in children undergoing HSCT. They revealed that high concentrations of human beta-defensin 2 prior to transplantation in patients with high abundances of *Lactobacilli* associated with moderate to severe aGvHD and exhibited high mortality. On the contrary, high abundance of obligate anaerobes, including *Ruminococcaceae*, associated with no or mild aGvHD and low mortalilty[9]. Biagi et al[10] described a gut microbial signature (i.e., depletion of *Blautia* and abundance of *Fusobacterium*) predictive for developing aGvHD in children undergoing HSCT. A final study investigated the effect of chemotherapy on the gut microbiota in ALL patients. ALL patients exposed to chemotherapy resulted in a decrease of the gut microbiota diversity. Interestingly, mucolytic Gram-positive bacteria, including *Ruminococcus gnavus* and *Ruminococcus torques*, were abundantly present during the chemotherapy regimen, which may contribute to the development of gastrointestinal complications in ALL children following chemotherapy[11].

Neurological disorders

Two papers explored the faecal microbiome in children with autism spectrum disorder (ASD). Arnold et al[12] investigated the benefit of probiotics in children with ASD and gastrointestinal symptoms. Outcome improvement significantly correlated with abundance of *Lactobacillus* without observable changes to microbiota composition and diversity[12]. Variation of maternal

gut microbiota may increase the risk of ASD in the offspring. Li et al[13] examined gut microbial signatures in children and their mothers with the aim to identify bacterial biomarkers with discriminative power. Mothers of ASD children had more *Proteobacteria*, *Moraxellaceae* and *Acinetobacter* than mothers of healthy children. Interestingly, ASD children carried unique bacterial biomarkers, including *Alcaligenaceae*, *Enterobacteriaceae* and *Clostridium*. The identified microbial mother-child patterns may be important for risk assessment and prevention of ASD *via* microbiota modulation[13]. A final study explored the gut microbiota in children with attention-deficit/hyperactivity disorder (ADHD) and showed that significant microbial differences (i.e., reduction of *Veillonellaceae* and *Faecalibacterium*) in ADHD children may play a role in gut-brain axis alterations and in this way could contribute to ADHD symptoms[14].

Other diseases

Chronic kidney disease (CDK) is associated with high risk of cardiovascular disease. Hsu et al[15] investigated the correlation between gut microbiota-dependent metabolites and the cardiovascular risk in children with CKD. They highlighted that microbial-derived methylamines associated with increased risk for cardiovascular diseases in pediatric CKD but warranted that further studies are necessary for usage of these microbial markers in CKD progression[15]. The relationship between pulmonary tuberculosis and gut microbial homeostasis is still poorly understood in the pediatric population. Li et al[16] shed more light on gut microbial signatures present in children with pulmonary tuberculosis. Based on their findings, they hypothesized that gut dysbiosis, characterized by *Prevotella* and *Enterococcus* abundance and a decrease of *Bifidobacteriaceae* and *Ruminococcaceae*, in children with tuberculosis affects the pathogenesis of the disease by dysregulation of the hosts' immune status *via* the gut-lung axis[16]. Kortekangas et al[17] studied whether common childhood infections, i.e., gastroenteritis and respiratory tract infections (as morbidity) predict gut microbiota composition. The authors hypothesized that gastrointestinal infections would be predictors for lower microbiota maturity and diversity. However, their findings showed only lower maturity at 12 months after recent diarrhoea. Respiratory Infections at the age of 12 months caused on the contrary increased microbiota diversity. Morbidity symptoms seem to be associated with changes in microbial community composition and influence abundance of certain species. However, there was no clear consistent pattern in these associations and therefore no conclusion could be drawn that reduction in disease burden would lead to a healthier microbiota environment or the other way around that that influencing the microbiota environment would impact on disease burden[17].

IMPACT OF ANTIBIOTIC TREATMENT ON THE PEDIATRIC GUT MICROBIOTA

The pediatric gut microbiota is established during the first years of life, representing a critical time window where the gut microbiota is especially vulnerable to external influences, including antibiotics. Coker et al[18] evaluated the potential impact of intrapartum antibiotic usage on the infant gut microbiota in the first year of life. Exposure to intrapartum antibiotics associated with lower microbial diversity, reduction of *Bacteroidetes* and *Bifidobacterium* taxa and a significant increase of *Veillonella*[18]. Another study investigated the effect of intrapartum antibiotics on the oral microbiome composition. Phyla *Actinobacteria* and *Bacteroidetes* were more abundant after intrapartum antibiotic exposure whereas *Lactobacillus* genera were more dominant in neonates not exposed to antimicrobial agents. Further function analysis demonstrated that LPS biosynthesis and amino acid metabolic function were enriched in neonates exposed to antibiotics while carbohydrate metabolic pathways were more abundant in the group without antimicrobial treatment. They concluded that intrapartum antibiotic treatment is a key regulator of the initial neonatal oral microbiota[19]. Early antibiotic exposure may also have a negative impact on bacterial composition, causing dysbiosis and thus increasing the risk for disease development. Zhou et al[20] showed that perinatal antibiotic treatment induced dysbiosis in the mother's vagina and the neonatal gut, characterized by a significant decrease of *Lactobacillus* abundance. Furthermore, they also suggested an association between perinatal antibiotic exposure and the risk for early-onset sepsis in infants[20]. Four other research papers[21-24] associated exposure of antibiotics to the risk of overweight,

development of asthma, allergic rhinitis, hypertension or celiac disease in children, further providing support for a conscious approach regarding antimicrobial usage in early childhood. On the contrary, antimicrobial usage can also have benficial effects in the treatment of disease. One study investigated the impact of metronidazole, with or without azithromycin, on the microbiota composition in pediatric CD and whether certain microbial features can act as predictors for CD remission. Both antimicrobial regimens lead to distinct microbiota signatures in pediatric CD at remission, but the authors warranted that larger cohorts are necessary to confirm these findings[25].

IMPACT OF NUTRITIONAL INTERVENTION ON THE PEDIATRIC GUT MICROBIOTA

Twelve papers were identified investigating the impact of nutritional intervention on the infant gut microbiota. Kamng'ona et al[26] described the effect of lipid-based nutrient supplements (LNSs), such as multiple micronutrients or iron and folic acid, on mature infant microbiota composition. Supplements were given to mothers during pregnancy and 6 months postpartum and to their infants from 6 to 18 months. Prenatal and postnatal LNS intake influenced gut microbiota diversity at 18 months of age, but did not altered microbiota maturation[26]. A second study publishing results from the same study cohort looked at additional environmental exposures, like stool sample collection (dry or wet), maternal education, water source, domestic animals, maternal HIV status, which could influence microbiota composition. The results showed that adverse environmental exposures affect the abundance of several bacterial OTU´s and genera. Low maternal education is furthermore associated with higher maturity and diversity. The authors further point out that these adverse environmental factors are indirectly reflecting the socio economic status and suggested that improvement of these environmental factors could have an important impact on health outcome[27]. Three studies described nutritional interventions during pregnancy or early life. Drall et al[28] looked at gut microbiome profile differences between exclusively breastfed-children, partially-breastfed-children and formula-fed children at the age of 2-4 months who were colonized with *Clostridioides difficile*. They showed that *C. difficile* colonisation was associated with a different gut microbiome in exclusively breast feed *vs.* exclusively formula fed children. In exclusively breast-fed children, an abundance of *Firmicutes* and *Proteobacteria* and less *Bifidobacteria* was observed. In formula fed infants, the microbial flora did not adapt to *Clostridium* infection suggesting that these infants are more prone to symptoms when colonized with *C. difficile*. Mancino et al[29] studied the transfer of *Bifidobacteria* from mother to child in an animal model. *Bifidobacteria* are the most abundant group in the gut microbiota of healthy infants. This study showed mother to pup transmission *via* the vertical route, but very interestingly, the same *Bifidobacterium* strain was also found in mother and pup after caesarean section. This could possibly suggest existence of colonization at preterm level[29]. Moossavi et al[30] investigated the influence of maternal and early life factors on microbiota composition and variation on mother-infant dyads from the CHILD cohort. Milk microbiota at 3-4 months of age were inversely dominated by *Proteobacteria* and *Firmicutes*. Composition was associated with maternal factors as for example BMI, parity, mode of delivery and breast-feeding practices. An interesting finding, which needs more investigation, is that pumped breast milk is associated with enrichment of potential pathogens and depletion of *Bifidobacteria* in a sex-dependent manner. This finding supports the retrograde inoculation hypothesis whereby infant oral cavity impacts on milk microbiota[30]. A paper written by Azad[31] summarizes the results of the same CHILD cohort study on the role of bioactives and microbiota in infant feeding. Breastfeeding was associated with lower richness and diversity of gut microbiota at 3-4 month of age with relative abundance of *Bifidobacteria*. This probably reduces the risk of obesity later on. In infants with risk of overweight there was abundance of *Lachnospiracae*[31]. Robinson et al[32] investigated the differences in gut microbiota composition in pregnant women with and without ketonuria at 16 weeks gestation. They concluded that the genus *Roseburia* is highly abundant in the gut microbiota of pregnant women with ketonuria, which is a butyrate producing bacterium increasing serum ketone levels. Hu et al[33] showed in a mouse model that time restricted feeding during childhood induced altered microbiota differences in diversity and specific groups of bacteria[33]. Two studies compared the effect of enteral *vs.* parenteral nutrition. Kaplan et al[34] found unexpected weak anti-B antibodies in 2 patients

with group O on parental nutrition and specific enteral feeds. Parental nutrition affects microbiota composition by reducing *Firmicutes* and increasing *Bacteroides* and *Proteobacteria*. This could be the cause of microbial dysbiosis which has an effect on the immune system but the authors warrant further study[34]. D´Amico et al[35] published a paper on promotion of gut microbiome homeostasis recovery after hematopoietic stem cell transplantation (HSCT) with enteral feeding in comparison to parenteral nutrition. Prompt recovery of structural and functional gut microbiota was only observed in the enteral nutrition group, possibly reducing the risk of systemic infections and graft versus host disease onset[35]. El Manouni el Hassani and colleagues[36] analyzed the effect of a daily intake of the *Lactobaccilus casei* strain Shirota (LcS) on microbial diversity and dynamics in healthy children (aged 12-18 years) from the Netherlands. They concluded that LcS ingestion did not result in a more diverse and stable gut microbiota composition[36]. Two final studies described study protocols for nutritional intervention in children. Mostafa et al[37] published a proof-of-concept study where they will look at the use of microbiota directed complementary food in the treatment of moderate malnutrition in Bangladesh. Worldwide 33 million children are affected by malnutrition, of whom 2 million children in Bangadesh. Weight gain, microbiota composition and biomarkers will be analyzed at baseline (start of intervention), after 1 month, 3 months (end of intervention), 1 month after the end of the intervention and every 6 months for 4 years[37]. Another study protocol described by Lind et al[38] will investigate the impact of protein reduced Nordic diet on faecal microbial composition. The diet comprises increased intake of fruits, berries, vegetables and whole grain and a decrease in the intake of sweets, dairy products, meat and poultry. The children will be randomly allocated in the Nordic Food group or the regular diet group. At age of 6-18 months, fecal microbial composition will be analyzed[38].

ROLE OF GUT MICROBIOTA IN EARLY INFANCY, GROWTH AND DEVELOPMENT

Thirteen studies fulfilled our selection criteria for the role of microbiota in early infancy and growth.

Four of them dealt with microbiota features in pregnancy and the effect on mother and new-born child. The paper by Avershina et al[39] focussed on spore-forming bacteria in the gut of mother-child pairs selected from the IMPACT study cohort in Norway. These bacteria (mainly *Clostridium*) comprise a large part of the human gut microbiota, but they are difficult to culture. The investigators developed a new culture-independent DNA technique [based on *16S rRNA* gene sequencing after a two-step purification technique with ethanol and ethidium monoazide (EMA)]. The results indicated a low abundance of endospore forming species shared between mothers and their children suggesting that these bacteria are mainly acquired from the environment[39]. Tanabe et al[40] investigated the association between the maternal microbiome and the prevalence of dermatitis in early infancy. They concluded that the diversity of Proteobacteria and relative abundance of Acinetobacteria were reduced in maternal faeces during pregnancy in cases of dermatitis in infancy, suggesting that this early trigger could be a good predictor of subsequent allergy and allergic march through infancy[40]. Another study from the same research group investigated the association between gut microbiota composition and metabolism *via* glycoalbumin level during pregnancy in healthy Japanese women. They found no evident differences in microbiota composition, but they indicated that their study was limited in power so further larger studies are required[41]. Sato et al[42] showed that maternal gut microbiota are associated to new-born anthropometrics in a sex-specific manner. Genus *Parabacteroides* and *Eggerthella* showed negative associations with new-born head circumference and weight, respectively in males. A higher proportion of *Streptococcus* was associated with smaller anthropometrics in females. These findings suggest that maternal microbiome is an important factor for intrauterine growth[42]. One paper and one protocol looked at the association between microbiome and child neurological development. Leong et al[43] presented a protocol to study the epigenetic influences on neurodevelopment at 11 years of age [longitudinal peri/postnatal epigenetic twin study (PETS@11)]. This analysis will include questionnaires, blood, faecal samples, and brain MRI-scans[43]. Atukunda et al[44] performed a follow-up education trial in Uganda looking at child development, growth, and microbiota. The trial included mother-child pairs recruited when the children were 6-8 months and divided in an intervention group where mothers received

nutrition, stimulation and hygiene education and a control group with routine health care. Interestingly, gut microbiota composition did not differ significantly between both groups[44]. Korpela et al[45] published a cohort profile from the Finnish Early life Microbiota (HELMi) longitudinal birth cohort consisting of healthy term infants born in 2016-2018, mainly in the capital region of Finland. The intestinal microbiota development is characterized based on faecal samples and extensive online questionnaire that collected data at weekly to monthly interval on diet, other exposures, family lifestyle, health, and growth of the child. Motor and cognitive screening was performed at 18 months of age. Infant DNA, mothers breast milk and parental samples were collected. Findings to date do not yet include microbial data[45]. Li et al[46] looked at the impact of delivery mode (vaginal *vs.* caesarean section) in very low birth weight infants´ microbiome of the neonatology intensive care from the Shenzhen University Hospital in China. The results demonstrated that oral bacterial communities were dominated by Proteobacteria in both groups. In the vaginal delivery infants, genera *Ureaplasma* and *Pantoea* were more prevalent, whereas *Corynebacterium*, *Methylobacterium* and *Variovorax* were more prevalent in caesarean born infants. There were also metabolic differences (mainly vitamin and amino-acid pathways) between the different modes of delivery[46]. The group of Huang (Shengzen University Hospital, China)[47] also described the characteristics of intestinal microbiota in very low birth weight infants with extrauterine growth restriction (EUGR). The intestinal bacterial communities of EUGR infants are dominated by *Proteobacteria*. The relative abundance of *Aeromicrobium* and *Serratia* is decreased, whereas genera *Parabacteroides*, *Ruminococcus*, *Blautia* and *Aeromonas* were more prevalent[47]. Moran-Ramos et al[48] looked at environmental and intrinsic factors shaping gut microbiota composition and diversity and its relation to metabolic health in children and early adolescence. Microbiota of 926 children (ORSMEC cohort) aged 6-12 years in Latin America were characterised. Fortheen clinical and environmental co-variates were identified explaining 15,7% of inter-individual gut microbial variation. Extrinsic factors, such as socioeconomic status, showed major influence on the most abundant taxa. Age was positively correlated to higher diversity in normal weight children. The authors concluded that these results will contribute to a better understanding of gut microbiome and ultimately develop therapeutic approaches to improve metabolic status[48]. Rouhani et al[49] concluded that diarrhoea is a potential cause and consequence of reduced gut microbial diversity among undernourished children in Peru. Children who were still severely stunted at time of sampling had the greatest diarrhoea-associated reductions in diversity and the slowest recovery. Increased diversity was, on the other hand, predictive of reduced, subsequent diarrheal episodes[49]. Another study showed that bacteriophages isolated from Bangladeshi stunted children (< 38 months) can regulate gut bacterial communities in an age-specific manner. Stunted children harbor distinct bacteriophages relative to their non-stunted counterparts. Proteobacteria from non-stunted children increased in the presence of phages from younger stunted children, suggesting that phages could contribute to the bacterial community changes observed[50]. *Campylobacter* infection is associated with impaired growth of children, also in the absence of symptoms. Rouhani et al[51] studied the associations between *Campylobacter* infection, linear growth, and fecal microbial community features in a prospective birth cohort with a high burden of diarrhea and stunting in the Amazonian lowlands of Peru. As *Campylobacter* infection was common in this cohort, clear disruptions in microbial communities were noted which could help explain the observed effects of asymptomatic infections on growth in early life[51].

CONCLUSIONS

In this review, evidence was given for the role of gut dysbiosis in a wide spectrum of diseases in children. Substantial progress has also been made in the understanding of the impact on antimicrobial treatment and nutritional intervention on microbial composition in childhood health and development. As the microbiota establishes during childhood, this may be the prime time for microbiota interventions for health promotion and/or disease prevention. It is therefore crucial to further unveal pediatric microbial gut signatures in health and disease and to identify the underlining mechanisms and confounding factors involved in disease onset and development in children.

Conflict of Interest

The authors declare no conflict of interest.

REFERENCES

1. Sila S, Jelić M, Trivić I, Tambić Andrašević A, Hojsak I, Kolaček S. Altered gut microbiota is present in newly diagnosed pediatric patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2020; 70: 497-502.
2. Kansal S, Catto-Smith AG, Boniface K, Thomas S, Cameron DJ, Oliver M, Alex G, Kirkwood CD, Wagner J. Variation of gut mucosal microbiome with anti-Saccharomyces cerevisiae antibody status in pediatric Crohn disease. J Pediatr Gastroenterol Nutr 2019; 69: 696-703.
3. Zhao Y, Zhou J, Liu J, Wang Z, Chen M, Zhou S. Metagenome of gut microbiota of children with nonalcoholic fatty liver disease. Front Pediatr 2019; 7: 518.
4. Chen X, Sun H, Jiang F, Shen Y, Li X, Hu X, Shen X, Wei P. Alteration of the gut microbiota associated with childhood obesity by 16S rRNA gene sequencing. Peer J 2020; 8: e8317.
5. Miao R, Wan C, Wang Z. The relationship of gastric microbiota and Helicobacter pylori infection in pediatrics population. Helicobacter 2020; 25: e12676.
6. Paun A, Yau C, Meshkibaf S, Daigneault MC, Marandi L, Mortin-Toth S, Bar-Or A, Allen-Vercoe E, Poussier P, Danska JS. Association of HLA-dependent islet autoimmunity with systemic antibody responses to intestinal commensal bacteria in children. Sci Immunol 2019; 4: pii: eaau8125.
7. Song Y, Gyarmati P. Microbiota changes in a pediatric acute lymphocytic leukemia mouse model. Microbiologyopen 2020; 9: e982.
8. Kelly MS, Ward DV, Severyn CJ, Arshad M, Heston SM, Jenkins K, Martin PL, McGill L, Stokhuyzen A, Bhattarai SK, Bucci V, Seed PC. Gut colonization preceding mucosal barrier injury bloodstream infection in pediatric hematopoietic stem cell transplantation recipients. Biol Blood Marrow Transplant 2019; 25: 2274-2280.
9. Ingham AC, Kielsen K, Cilieborg MS, Lund O, Holmes S, Aarestrup FM, Müller KG, Pamp SJ. Specific gut microbiome members are associated with distinct immune markers in pediatric allogeneic hematopoietic stem cell transplantation. Microbiome 2019; 7: 131.
10. Biagi E, Zama D, Rampelli S, Turroni S, Brigidi P, Consolandi C, Severgnini M, Picotti E, Gasperini P, Merli P, Decembrino N, Zecca M, Cesaro S, Faraci M, Prete A, Locatelli F, Pession A, Candela M, Masetti R. Early gut microbiota signature of aGvHD in children given allogeneic hematopoietic cell transplantation for hematological disorders. BMC Med Genomics 2019; 12: 49.
11. Rajagopala SV, Singh H, Yu Y, Zabokrtsky KB, Torralba MG, Moncera KJ, Frank B, Pieper R, Sender L, Nelson KE. Persistent gut microbial dysbiosis in children with acute lymphoblastic leukemia (ALL) during chemotherapy. Microb Ecol 2019; 79: 1034-1043.
12. Arnold LE, Luna RA, Williams K, Chan J, Parker RA, Wu Q, Hollway JA, Jeffs A, Lu F, Coury DL, Hayes C, Savidge T. Probiotics for gastrointestinal symptoms and quality of life in autism: a placebo-controlled pilot trial. J Child Adolesc Psychopharmacol 2019; 29: 659-669.
13. Li N, Yang J, Zhang J, Liang C, Wang Y, Chen B, Zhao C, Wang J, Zhang G, Zhao D, Liu Y, Zhang L, Yang J, Li G, Gai Z, Zhang L, Zhao G. Correlation of gut microbiome between ASD children and mothers and potential biomarkers for risk assessment. Genomics Proteomics Bioinformatics 2019; 17: 26-38.
14. Wan L, Ge WR, Zhang S, Sun YL, Wang B, Yang G. Case-control study of the effects of gut microbiota composition on neurotransmitter metabolic pathways in children with attention deficit hyperactivity disorder. Front Neurosci 2020; 14: 127.
15. Hsu CN, Chang-Chien GP, Lin S, Hou CY, Lu PC, Tain YL. Association of trimethylamine, trimethylamine N-oxide, and dimethylamine with cardiovascular risk in children with chronic kidney disease. J Clin Med 2020; 9. pii: E336.
16. Li W, Zhu Y, Liao Q, Wang Z, Wan C. Characterization of gut microbiota in children with pulmonary tuberculosis. BMC Pediatr 2019; 19: 445.
17. Kortekangas E, Young R, Cheung YB, Fan YM, Jorgensen JM, Kamng'ona AW, Chaima D, Ashorn U, Dewey KG, Maleta K, Ashorn P. A prospective study on child morbidity and gut microbiota in rural Malawi. J Pediatr Gastroenterol Nutr 2019; 69: 431-437.
18. Coker MO, Hoen AG, Dade E, Lundgren S, Li Z, Wong AD, Zens MS, Palys TJ, Morrison HG, Sogin ML, Baker ER, Karagas MR, Madan JC. Specific class of intrapartum antibiotics relates to maturation of the infant gut microbiota: a prospective cohort study. BJOG 2020; 127: 217-227.
19. Li H, Xiao B, Zhang Y, Xiao S, Luo J, Huang W. Impact of maternal intrapartum antibiotics on the initial oral microbiome of neonates. Pediatr Neonatol 2019; 60: 654-661.
20. Zhou P, Zhou Y, Liu B, Jin Z, Zhuang X, Dai W, Yang Z, Feng X, Zhou Q, Liu Y, Xu X, Zhang L. Perinatal antibiotic exposure affects the transmission between maternal and neonatal microbiota and is associated with early-onset sepsis. mSphere 2020; 5. pii: e00984-19.
21. Jess T, Morgen CS, Harpsøe MC, Sørensen TIA, Ajslev TA, Antvorskov JC, Allin KH. Antibiotic use during pregnancy and childhood overweight: A population-based nationwide cohort study. Sci Rep 2019; 9: 11528.
22. Galla S, Chakraborty S, Cheng X, Yeo JY, Mell B, Chiu N, Wenceslau CF, Vijay-Kumar M, Joe B. Exposure to amoxicillin in early life is associated with changes in gut microbiota and reduction in blood pressure: findings from a study on rat dams and offspring. J Am Heart Assoc 2020; 9: e014373.
23. Ni J, Friedman H, Boyd BC, McGurn A, Babinski P, Markossian T, Dugas LR. Early antibiotic exposure and development of asthma and allergic rhinitis in childhood. BMC Pediatr 2019; 19: 225.
24. Dydensborg Sander S, Nybo Andersen AM, Murray JA, Karlstad Ø, Husby S, Størdal K. Association between antibiotics in the first year of life and celiac disease. Gastroenterology 2019; 156: 2217-2229.

25. Sprockett D, Fischer N, Boneh RS, Turner D, Kierkus J, Sladek M, Escher JC, Wine E, Yerushalmi B, Dias JA, Shaoul R, Kori M, Snapper SB, Holmes S, Bousvaros A, Levine A, Relman DA. Treatment-specific composition of the gut microbiota is associated with disease remission in a pediatric Crohn's disease cohort. Inflamm Bowel Dis 2019; 25: 1927-1938.
26. Kamng'ona AW, Young R, Arnold CD, Patson N, Jorgensen JM, Kortekangas E, Chaima D, Malamba C, Ashorn U, Cheung YB, Ashorn P, Maleta K, Dewey KG. Provision of lipid-based nutrient supplements to mothers during pregnancy and 6 months postpartum and to their infants from 6 to 18 months promotes infant gut microbiota diversity at 18 months of age but not microbiota maturation in a rural Malawian setting: secondary outcomes of a randomized trial. J Nutr 2020. pii: nxz298.
27. Kortekangas E, Kamng'ona AW, Fan YM, Cheung YB, Ashorn U, Matchado A, Poelman B, Maleta K, Dewey KG, Ashorn P. Environmental exposures and child and maternal gut microbiota in rural Malawi. Paediatr Perinat Epidemiol 2020; 34: 161-170.
28. Drall KM, Tun HM, Morales-Lizcano NP, Konya TB, Guttman DS, Field CJ, Mandal R, Wishart DS, Becker AB, Azad MB, Lefebvre DL, Mandhane PJ, Moraes TJ, Sears MR, Turvey SE, Subbarao P, Scott JA, Kozyrskyj AL. Clostridioides difficile colonization is differentially associated with gut microbiome profiles by infant feeding modality at 3-4 months of age. Front Immunol 2019; 10: 2866.
29. Mancino W, Duranti S, Mancabelli L, Longhi G, Anzalone R, Milani C, Lugli GA, Carnevali L, Statello R, Sgoifo A, van Sinderen D, Ventura M, Turroni F. Bifidobacterial transfer from mother to child as examined by an animal model. Microorganisms 2019; 7. pii: E293.
30. Moossavi S, Sepehri S, Robertson B, Bode L, Goruk S, Field CJ, Lix LM, de Souza RJ, Becker AB, Mandhane PJ, Turvey SE, Subbarao P, Moraes TJ, Lefebvre DL, Sears MR, Khafipour E, Azad MB. Composition and variation of the human milk microbiota are influenced by maternal and early-life factors. Cell Host Microbe 2019; 25: 324-335.
31. Azad MB. Infant feeding and the developmental origins of chronic disease in the CHILD cohort: Role of human milk bioactives and gut microbiota. Breastfeed Med 2019; 14: S22-S24.
32. Robinson H, Barrett H, Gomez-Arango L, McIntyre HD, Callaway L, Dekker Nitert M. Ketonuria is associated with changes to the abundance of Roseburia in the gut microbiota of overweight and obese women at 16 weeks gestation: A cross-sectional observational study. Nutrients 2019; 11: pii: E1836.
33. Hu D, Ye Y, Mao Y, Liao W, Xu W. Time-restricted feeding during childhood has persistent effects on mice commensal microbiota. Ann Transl Med 2019; 7: 556.
34. Kaplan A, Gabert KA, Yazer MH. Unexpectedly weak anti-B in 2 group O pediatric patients on parenteral nutrition and disease specific supplemental enteral feeds. Lab Med 2019. pii: lmz057.
35. D'Amico F, Biagi E, Rampelli S, Fiori J, Zama D, Soverini M, Barone M, Leardini D, Muratore E, Prete A, Gotti R, Pession A, Masetti R, Brigidi P, Turroni S, Candela M. Enteral nutrition in pediatric patients undergoing hematopoietic SCT promotes the recovery of gut microbiome homeostasis. Nutrients 2019; 11. pii: E2958.
36. El Manouni El Hassani S, de Boer NKH, Jansen FM, Benninga MA, Budding AE, de Meij TGJ. Effect of daily intake of Lactobacillus casei on microbial diversity and dynamics in a healthy pediatric population. Curr Microbiol 2019; 76: 1020-1027.
37. Mostafa I, Nahar NN, Islam MM, Huq S, Mustafa M, Barratt M, Gordon JI, Ahmed T. Proof-of-concept study of the efficacy of a microbiota-directed complementary food formulation (MDCF) for treating moderate acute malnutrition. BMC Public Health 2020; 20: 242.
38. Lind T, Johansson U, Öhlund I, Lindberg L, Lönnerdal B, Tennefors C, Hernell O. Study protocol: optimized complementary feeding study (OTIS): a randomized controlled trial of the impact of a protein-reduced complementary diet based on Nordic foods. BMC Public Health 2019; 19: 134.
39. Avershina E, Larsen MG, Aspholm M, Lindback T, Storrø O, Øien T, Johnsen R, Rudi K. Culture dependent and independent analyses suggest a low level of sharing of endospore-forming species between mothers and their children. Sci Rep 2020; 10: 1832.
40. Tanabe H, Sakurai K, Kato T, Kawasaki Y, Nakano T, Yamaide F, Taguchi-Atarashi N, Watanabe M, Ochiai S, Ohno H, Fukuoka H, Shimojo N, Mori C. Association of the maternal microbiome in Japanese pregnant women with the cumulative prevalence of dermatitis in early infancy: A pilot study from the Chiba study of mother and child health birth cohort. World Allergy Organ J 2019; 12: 100065.
41. Sakurai K, Kato T, Tanabe H, Taguchi-Atarashi N, Sato Y, Eguchi A, Watanabe M, Ohno H, Mori C. Association between gut microbiota composition and glycoalbumin level during pregnancy in Japanese women: Pilot study from Chiba study of mother and child health. J Diabetes Investig 2020; 11: 699-706.
42. Sato Y, Sakurai K, Tanabe H, Kato T, Nakanishi Y, Ohno H, Mori C. Maternal gut microbiota is associated with newborn anthropometrics in a sex-specific manner. J Dev Orig Health Dis 2019; 10: 659-666.
43. Leong P, Loke YJ, Saffery R, Silk T, Burnett A, Josev E, Scurrah K, Theda C, Czajko A, Pua EP, Seal ML, Craig JM. Epigenetic influences on neurodevelopment at 11 years of age: protocol for the longitudinal peri/postnatal epigenetic twins study at 11 years of age (PETS@11). Twin Res Hum Genet 2019; 22: 446-453.
44. Atukunda P, Muhoozi GKM, van den Broek TJ, Kort R, Diep LM, Kaaya AN, Iversen PO, Westerberg AC. Child development, growth and microbiota: follow-up of a randomized education trial in Uganda. J Glob Health 2019; 9: 010431.
45. Korpela K, Dikareva E, Hanski E, Kolho KL, de Vos WM, Salonen A. Cohort profile: Finnish health and early life microbiota (HELMi) longitudinal birth cohort. BMJ Open 2019; 9: e028500.
46. Li H, Zhang Y, Xiao B, Xiao S, Wu J, Huang W. Impacts of delivery mode on very low birth weight infants' oral microbiome. Pediatr Neonatol 2020; 61: 201-209.
47. Li H, He Z, Gao D, Lv Y, Zhou Q, Xiao B, Huang W. Characteristics of the Intestinal microbiota in very low birth weight infants with extrauterine growth restriction. Front Pediatr 2019; 7: 99.

48. Moran-Ramos S, Lopez-Contreras BE, Villarruel-Vazquez R, Ocampo-Medina E, Macias-Kauffer L, Martinez-Medina JN, Villamil-Ramirez H, León-Mimila P, Del Rio-Navarro BE, Ibarra-Gonzalez I, Vela-Amieva M, Gomez-Perez FJ, Velazquez-Cruz R, Salmeron J, Reyes-Castillo Z, Aguilar-Salinas C, Canizales-Quinteros S. Environmental and intrinsic factors shaping gut microbiota composition and diversity and its relation to metabolic health in children and early adolescents: a population-based study. Gut Microbes 2020; 23: 1-18.
49. Rouhani S, Griffin NW, Yori PP, Gehrig JL, Olortegui MP, Salas MS, Trigoso DR, Moulton LH, Houpt ER, Barratt MJ, Kosek MN, Gordon JI. Diarrhea as a potential cause and consequence of reduced gut microbial diversity among undernourished children in Peru. Clin Infect Dis 2019; pii: ciz905. doi: 10.1093/cid/ciz905. [Epub ahead of print].
50. Khan Mirzaei M, Khan MAA, Ghosh P, Taranu ZE, Taguer M, Ru J, Chowdhury R, Kabir MM, Deng L, Mondal D, Maurice CF. Bacteriophages isolated from stunted children can regulate gut bacterial communities in an age-specific manner. Cell Host Microbe 2020; 27: 199-212.
51. Rouhani S, Griffin NW, Yori PP, Olortegui MP, Siguas Salas M, Rengifo Trigoso D, Moulton LH, Houpt ER, Barratt MJ, Kosek MN, Gordon JI. Gut microbiota features associated with Campylobacter burden and postnatal linear growth deficits in a Peruvian birth cohort. Clin Infect Dis 2019; pii: ciz906.