

Review Article

Intraindividual double burden of malnutrition: The contribution of the infant gut microbiome

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The prevalence of the double burden of malnutrition in society is well known with the coexistence of undernutrition with an increase in overweight/obesity; this has been increasing globally with nutritional imbalances and infectious diseases being the major etiological factors. However, there is also the coexistence of inappropriate adiposity or metabolic dysfunction in an individual who appears currently undernourished by anthropometric standards (stunted or underweight); this is the intraindividual double burden of malnutrition. It could also occur in temporal sequence, as anthropometric overweight in an individual who has previously endured childhood undernutrition. IIDBM has increased the risk for diet-related non-communicable diseases over the past few decades, as it tracks into adulthood, warranting an urgent need for intervention and prevention. While gut dysbiosis has been associated with various forms of malnutrition, the early life gut microbiome composition and its related metabolites and regulatory factors, are possibly linked to the development of inflammatory and metabolic conditions in IIDBM. The possible underlying physiological mechanisms are reviewed here, working through host dietary influences, gut microbial metabolites, host inflammation and metabolic dysregulation. When validated experimentally and tested through appropriately designed randomised, controlled trials, these mechanistic insights will likely lead to development of preventive strategies.

Key Words: infant gut microbiome, intraindividual double burden of malnutrition, undernutrition, overnutrition, diet

THE DOUBLE BURDEN OF MALNUTRITION (DBM) IN CHILDHOOD

The Double Burden of Malnutrition (DBM) is now recognised as a global challenge, characterised by the coexistence of undernutrition along with overweight/obesity (OW/OB) or diet-related Non-Communicable Diseases (NCDs) (diabetes, cardiovascular disease, stroke) within individuals, households and populations and across the lifecourse.¹⁻³ Globally, the rates of undernutrition have been gradually declining in many countries; however, there has been a sudden increase in OW/OB and associated NCDs.¹ In India, the Comprehensive National Nutrition Survey (CNNS, 2016-2018) of children and the National Family Health Survey-5 (NFHS) definitively showed the presence of DBM (stunting and overweight) in Indian children and adolescents, which is now a public health concern.^{4,5}

Intraindividual DBM (IIDBM) is the co-occurrence of two or more types of malnutrition in an individual, which can occur across the life-course.¹ It represents the erosion of a comfortable clinical binary of evaluating an individual as either overfed or underfed based on anthropometric indices. With IIDBM, an apparently thin or stunted individual could also have high fat mass or metabolic biomarkers of NCD. Thus, in the CNNS,⁴ an analysis of thin or stunted children showed a high (>50%) prevalence of at least one biomarker of dysglycaemia and dyslipidaemia which would otherwise indicate a positive energy balance.⁶ This is perplexing yet evocative of the thin-yet-

fat phenotype that is observed in adult Indians and South Asians and is probably an early manifestation of this phenotype.⁷ Nevertheless, this is a unique paradox in children where undernutrition could reduce their physical and mental capacity while the adiposity would increase their risk for several NCDs. In a temporal frame, IIDBM could also manifest as the presence of later life OW/OB in an individual who was previously stunted from chronic undernutrition during childhood, although it cannot be ruled out if IIDBM was not already present during childhood stunting as either excess adiposity or metabolic overnutrition.¹ Since NCDs are the major cause of mortality in India with the majority of premature NCD deaths being preventable, along with alarming findings from CNNS data on IIDBM in Indian children, there is a critical need to develop new nutrition strategies to address IIDBM.^{6,8,9} Interestingly, IIDBM is not a problem unique to the 21st century. Waterlow reported his findings of fatty liver in children with kwashiorkor as far back as the 1940s.¹⁰ However, metabolic and mechanistic underpinnings of

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IIDBM remain fairly under-investigated even now.

There are several possible mechanisms related to IIDBM. Childhood stunting has been associated with impairment in fat oxidation with a net positive energy balance that is linked to adult obesity.¹¹ As stated above for Indian children, in low-and-middle-income countries (LMICs), metabolic obesity biomarker(s) have been observed to occur in more than half of anthropometrically undernourished and normal-weight Indian children and adolescents.⁶ The long-term effects of early life malnutrition can be due to various interconnected biological pathways that involve metabolic dysregulation, impaired insulin function and gut microbiome (GM) imbalance. The appearance of NCDs in individuals who have endured childhood undernutrition could also be due to an increase in metabolic load on a depleted metabolic capacity (for example, a lower glucose disposal due to a lower skeletal muscle mass) for homeostasis.²

The diagnosis of IIDBM must therefore advance from the sole use of anthropometry to the additional use of blood and other biomarkers. Specifically, although obesity can be assessed anthropometrically, metabolic obesity biomarkers such as abnormal blood sugar (fasting glucose, Hb1Ac), blood lipids (total cholesterol, triglycerides, LDL and HDL), altered body composition (increased body fat, lowered skeletal muscle) and fatty liver could be present well before the child becomes OW/OB. These biomarkers can be useful evaluation tools to help in the early detection and prevention of NCDs in children with undernutrition.

THE GUT MICROBIOME IN INFANCY AND CHILDHOOD

The association between a human being and their GM is symbiotic whereby the human host provides nutrition for the microbial community and the microbial population assists with essential functions for the human.¹² These functions could be aiding in immune system development, defence against enteric infection, assisting in energy metabolism and homeostasis.¹³ Obesity and inflammatory bowel disease have been extensively studied in relation to GM in humans and animals.¹³ GM alterations have been noted in both childhood undernutrition and obesity.^{14,15}

The establishment of the GM occurs early in life and is featured by a rapid patterned progression from birth to an adult-like state at around 2.5 years.¹⁶ Several factors affect the GM composition during this period; though post-natal factors such as mode of delivery, feeding type and antibiotic exposure can affect the infant GM development, prenatal factors that influence GM development are the least understood.¹⁷ Early-life nutrition is a major influencing factor in the development of the infant GM, and in that sense, infancy represents a critical window of opportunity for programming of future metabolic and immune health.^{17,18}

Metabolites that are produced/transformed by the GM

Metabolites are small molecules which are involved in the crosstalk between the GM and human host. They are intermediate/end products of GM metabolism and any changes, an increase or decrease, in specific obesity-related GM metabolites can affect various metabolic

pathways in the host predisposing to the development of obesity.¹⁹

Short chain fatty acids (SCFAs)

A GM population that has a low abundance of species producing short chain fatty acids (SCFAs), in particular acetate and lactate, has been reported to retard the “beiging” process (browning of white adipose tissue), thus bringing about a reduction in thermogenesis and causing metabolic inflammation with an increase in white adipose tissue (WAT) and bringing about a rise in adiposity (Figure 1).²⁰ Faecal analyses in obese children show significantly higher concentrations of acetate, propionate and butyrate as well as total SCFAs compared to normal-weight children; the concentration of total SCFAs was significantly associated with obesity and the BMI.²¹ Increased microbial production, shifts in microbial cross-feeding patterns or low mucosal absorption may be the reasons for the increased concentrations of faecal SCFAs.²² GM derived microbial metabolite butyrate was reported to regulate thermogenesis in BAT and WAT through the activation of lysine-specific demethylase (LSD1) and Uncoupling protein (UCP) in BAT and WAT.²⁰ Further, dietary supplementation with SCFAs (acetate, propionate, butyrate or their combination) significantly inhibited body weight gain in high-fat diet-induced obese mice. SCFAs regulated adipose lipid metabolism, promoted beige adipogenesis and altered the GM composition (specifically the Firmicutes to Bacteroidetes ratio). This additionally caused reduction in body weight by increasing triglyceride hydrolysis and free fatty acid (FFA) oxidation in the adipose tissue (Figure 1).²³ SCFAs such as butyrate, acetate, and propionate, produced by the fermentation of carbohydrates, can act in the liver and adipose tissue to decrease expression of peroxisome proliferator-activated receptor gamma (PPARG) which in turn increases fatty acid oxidation.²⁴

Tryptophan metabolites

GM-derived tryptophan metabolites (indole and indoxyl sulphate) in mice attenuated progression of fat mass gain and diet-induced obesity by downregulating expression of miR-181 cluster microRNAs in WAT. One of these tryptophan metabolites (indole) was also found to be reduced in the blood of obese children, pointing to the likelihood of these metabolites playing similar role in regulating adiposity in children (Figure 1).²⁵

Trimethylamine N-oxide (TMAO)

TMAO, a gut microbiota-derived metabolite, has been recently linked to increased atherosclerosis and cardiovascular risk.²⁶ Increase in circulating TMAO concentrations have been observed after the gut microbial metabolism of dietary L-carnitine and phosphatidylcholine-rich foods such as red meat, eggs and dairy products.²⁷ The TMAO concentrations in adults stratified according to BMI increased with BMI and were positively associated with visceral adiposity index and fatty liver index independently suggesting the potential role of TMAO as an early biomarker of adipose dysfunction and NAFLD which might help in identifying subjects at high risk of NAFLD.²⁷ Although there is no identifiable mechanistic

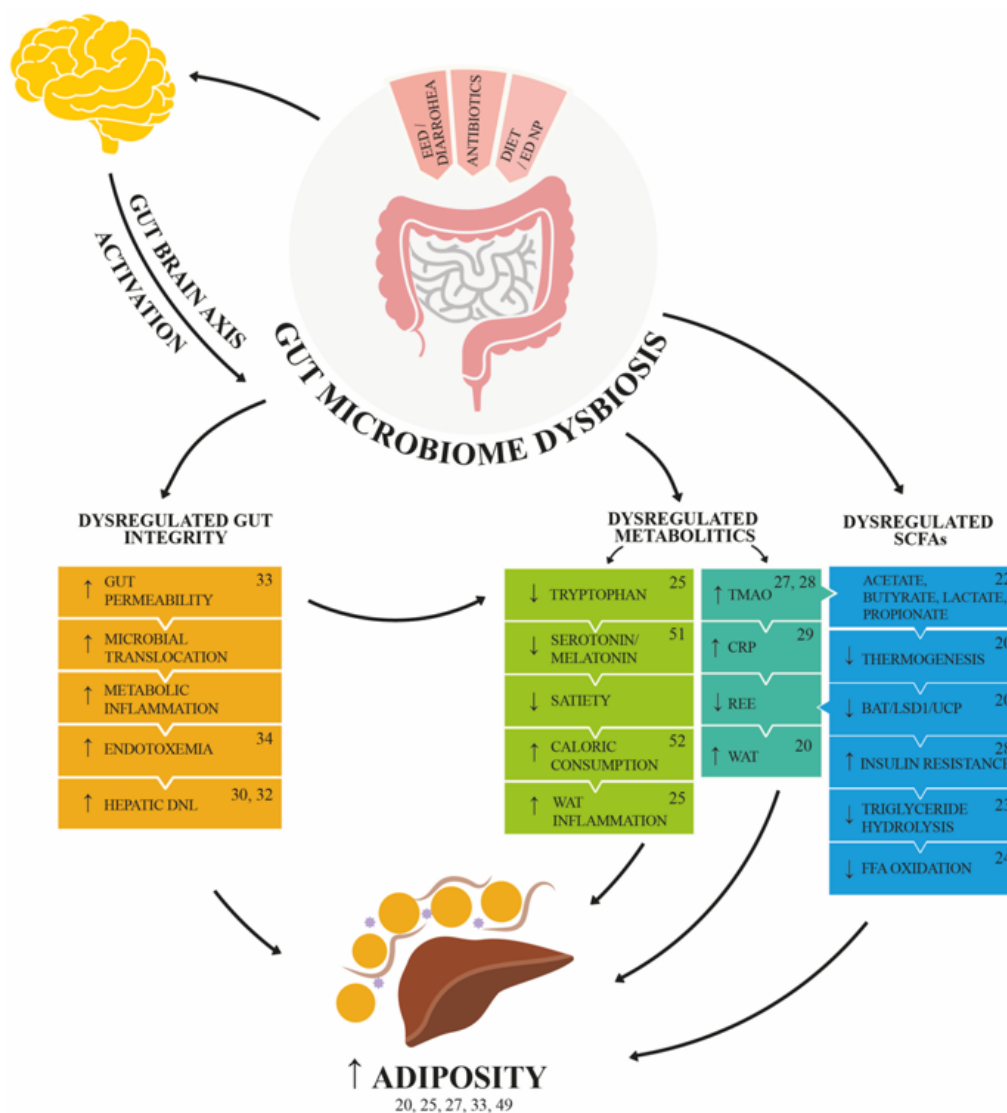


Figure 1. A compact overview of possible etiologies of IIDBM in relation to GM. Numbers in the superscript are references. GM: Gut microbiome; IIDBM: Intra-individual double burden of malnutrition; SCFAs: Short-chain-fatty-acids; EDNP: Energy dense nutrient poor; EED: Environmental enteric dysfunction; GIP: Glucose dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide 1; WAT: White adipose tissue; BAT: Brown adipose tissue; DNL: De novo lipogenesis; YMAO: Trimethylamine N-oxide; CRP: C-reactive peptide; REE: Resting energy expenditure; LSP1: Lysine specific demethylase 1; UCP: Uncoupling protein; FFA: Free fatty acid.

pathway linking increased TMAO concentrations with obesity, it is probable that flavin-containing monooxygenase 3 (FMO3), the enzyme that produces TMAO, could play a role in regulating obesity and “being” of white adipose tissue, and this in addition to increased hepatic insulin resistance due to higher TMAO concentrations can lead to obesity.²⁸ Increased chronic inflammation could be an additional contributor as a recent dose-response meta-analysis concluded that in humans, circulating TMAO and C-reactive peptide (CRP, an indicator of inflammation) exhibited a non-linear, positive association (Figure 1).²⁹

AN ETIOLOGICAL FRAMEWORK FOR IIDBM

There are many factors such as adverse early life exposures, poor nutrition, metabolic dysfunction and GM imbalances that can be attributed to the development of IIDBM. In terms of dietary influences, harking back to the historical report of the occurrence of fatty liver in children with kwashiorkor, these children were mostly

subsisting on sugarcane juice that was amply available to their mothers working in sugarcane fields.¹⁰ Current knowledge on hepatic de novo lipogenesis (DNL) helps explain this finding as fructose (from sugarcane juice containing sucrose: a glucose-fructose disaccharide), but not glucose, has recently been reported to potently induce basal hepatic DNL rates, albeit in healthy adult men, thereby providing a basis for hepatic fat deposition.³⁰ Dietary glucose and fructose also have different effects on fat metabolism with a greater reduction in fatty acid oxidation and greater lipid synthesis in response to an extra fructose diet compared with an extra glucose diet.³¹

Hepatic de novo lipogenesis and lipogenic diets

Mechanistically, chronic fructose consumption-induced intestinal barrier deterioration and associated inflammation have recently been implicated as a driver for fructose stimulated hepatic DNL.³² A mouse model showed that prolonged high fructose feeding caused intestinal barrier deterioration, increased circulating endotoxin concentra-

tions, liver inflammation, associated upregulation of the hepatic DNL pathway genes and liver steatosis. GM profile could aid in the maintenance of whereas GM dysbiosis could lead to deterioration of the intestinal barrier function.³³ Extending this line of reasoning, it seems plausible that apart from chronic fructose consumption, multiple other ways of damaging the intestinal barrier (either dietary through low fibre foods or pathogen-induced) and consequent endotoxemia may similarly lead to hepatic inflammation and an associated increase in hepatic DNL. On the other hand, dietary factors that either improve the intestinal barrier or reduce the inflammatory impact of the resultant low-grade endotoxemia should reduce hepatic inflammation and DNL. Evidence to that effect exists for omega-3 polyunsaturated fatty acid (n-3 PUFA). Supplementation with n-3 PUFA, for 8 weeks in healthy adults, resulted in an attenuated inflammatory response to a low-dose endotoxin challenge.³⁴ Additionally, adults with non-alcoholic fatty liver disease (NAFLD) have been reported to have low intakes of n-3 PUFA and n-3 PUFA has also been recommended as a nutrient supplement for improving NAFLD due to its beneficial effect on hepatic lipid metabolism and inflammation.³⁵ In children, intervention with modified PUFA has shown to be a safe and efficacious for the treatment of NAFLD.^{36,37}

Hepatic de novo lipogenesis, hepatic Insulin-like Growth Factor-I (IGF-I) production and linear growth

The liver is the primary site for the production of IGF-I.³⁸ NAFLD may further lead to low hepatic production of IGF-I in humans. This forms a conceptual basis for the impairment of linear growth in undernourished children with abnormally high liver fat. Though low circulating IGF-I concentrations have been reported with NAFLD, both in adults and in children, it should be noted that NAFLD patients are usually OW/OB.^{39,40} Future longitudinal studies on stunted children as well as children at high risk of developing NAFLD, with in-depth measurements of dietary, metabolic and GM associated parameters related to both over- and under-nutrition, are needed to test this etiological framework for IIDBM.

GM, overnutrition and adiposity

The simple, less diverse GM of young infants shifts to a more mature anaerobic microbiota high in *Bifidobacterium* and *Collinsella* by 6 months of age. A delayed acquisition, noted in C-section born infants and infants with shorter gestational duration, is linked with lower adiposity at 18 months of age.⁴¹ GM may contribute to overnutrition by enabling hydrolysis of indigestible polysaccharides to more absorbable monosaccharides and activation of lipoprotein lipase through direct action of the villous epithelium causing glucose to be rapidly adsorbed and excess fatty acid stored.⁴² GM in the first two years of life, as observed in a Norwegian birth cohort study, is highly predictive of later childhood BMI at age 12 when compared to BMI at two years of age underscoring the importance of GM being an early indicator of obesity.⁴³ The subset of IGM taxa associated with later childhood BMI was also linked with maternal obesity and excessive gestational weight gain. Abundance of *Bacteroides* posi-

tively correlated with BMI in the 1- and 2-year GM which are known to be influenced by environmental factors such as diet.^{43,44} Hence, dietary and other interventions can be targeted at high-risk children at an early stage to prevent later obesity.

Obesity-related studies have identified abundance of *Faecalibacterium prausnitzii* at 2 years as predictor of low childhood BMI; a higher abundance of *Streptococcus* in the first months of life with increased BMI and adiposity; and possibly a higher *Lactobacillus* and lower *Bacteroides* abundance in the first 3 months of age with higher risk for infant and child overweight, though studies on the latter shows mixed results.⁴³ High abundance of *Bacteroides fragilis* and low abundance of *Staphylococcus* in GM between the age of 3 weeks and 1 year were associated with higher risk of obesity in later life.⁴⁵ Furthermore, it was observed that obese children had a higher Firmicutes-to-Bacteroidetes ratio compared to lean children and lower *B. vulgatus* and high concentrations of *Lactobacillus spp.*¹⁵ Changes in Firmicutes and Bacteroidetes may be a significant indicator of childhood obesity and hence modification of GM using dietary manipulation and pre/probiotic formulations targeting these species could be a new strategy to prevent obesity. However, there is a lack of adequate definitive data on association of GM composition with adiposity; thus, additional studies involving heterogeneous populations are required to identify the exact bacterial taxa involved with adiposity and the effects of diet/dietary interventions on these obesity-related bacterial taxa.

Metabolic disorders such as obesity, type 2 diabetes (T2D) and NAFLD are characterised by alterations in the GM composition and its metabolites, which translocate across a disrupted intestinal barrier to affect various metabolic organs, such as the liver and adipose tissue, thereby contributing to metabolic inflammation, which in turn increases adiposity. The GM has recently been recognised as one of the contributing factors affecting insulin resistance. Inflammation, lipotoxicity, insulin sensitivity and gut dysbiosis are noted in individuals with NAFLD.⁴⁶

Interestingly, a recent systematic review on environmental enteric dysfunction (EED: a disease associated with child stunting, involving small intestine lining damage) and child stunting concluded that of the 5 domains of EED analysed by the authors (intestinal damage and repair, intestinal permeability and absorption, microbial translocation, intestinal inflammation and systemic inflammation), evidence for the link between intestinal inflammation, systemic inflammation and stunting was the strongest.⁴⁷ Similarly, in animal studies, consumption of high-fat diet has been reported to cause gut dysbiosis, increased epithelial permeability of the small intestines that facilitates leak of bacterial compounds and metabolites into the circulation (leaky gut) promoting inflammation and subsequently development of obesity, adiposity, insulin resistance and glucose intolerance preceding hyperglycemia.⁴⁸

Germ free (GF) mice are resistant to high-fat diet (HFD)-induced obesity despite a higher food intake.⁴⁹ This protection from diet-induced obesity is based on both increased fatty acid oxidation via upregulation of phosphorylated AMP-activated protein kinase (AMPK)

and its downstream regulators in skeletal muscle and liver and elevated expression of fasting-induced adipose factor (Fiaf), that inhibits lipoprotein lipase (LPL), thereby attenuating storage of liver-derived triglycerides in WAT.⁴⁹ From these observations, it seems plausible that gut dysbiosis-associated low-grade intestinal and systemic inflammation, experienced by undernourished children, could lead to later development of increased adiposity when energy-dense foods become available to these children.

The gut-brain axis

Dysbiosis in the GM is debated to contribute to Central Nervous System (CNS) disorders through the microbiota-gut-brain axis, which modulates various direct and indirect mechanistic pathways; endocrine pathways via cortisol secretion, immune pathways via cytokines production and neural pathways via the vagus and enteric nervous system signalling. GM dysbiosis (during stress) can interfere with the hypothalamus-pituitary-adrenal (HPA) axis signalling to increase secretion of cortisol which can alter gut permeability and barrier function. This could further contribute to GM dysbiosis and activate immune pathways leading to an increase in circulating cytokine concentrations levels that activate the vagus nerve signalling to modulate tryptophan metabolism by GM for synthesis of microbial neuroactive metabolites; indole, serotonin and melatonin thereby limiting the availability for the host and bacterial sugars.⁵⁰ Dysbiosis can affect serotonin concentrations levels and satiety leading to hunger, increased energy intake and fat storage.⁵¹ An unbalanced diet causing gut dysbiosis can trigger altered production of neurotransmitters, leading to overeating and weight gain.⁵² Gut microbiota plays a key regulatory role in both host metabolism and central appetite, which can modify host eating behaviour in metabolic and eating disorders such as obesity and malnutrition (Figure 1).⁵³

Infections and antibiotic usage

Dysbiosis due to the administration of subtherapeutic antibiotic therapy (STAT) during diarrhoea increased adiposity in young mice by amplifying concentration of glucose-dependent insulinotropic polypeptide (GIP), a metabolically active hormone involved in growth.⁵⁴ Antibiotic usage can cause long-term changes to the temporal maturation of GM and host responses to specific microbial signals with taxonomic changes that alter key genes functions involved in the metabolism of carbohydrates to SCFAs resulting in an increase in SCFAs causing alterations in the regulation of hepatic metabolism of lipids and cholesterol affecting host health and disease, typically long-term metabolic consequences affecting adiposity and bone development.⁵⁴ Several hypotheses exist for the mechanisms by which antibiotics modulate weight gain; increased ability of gut bacteria to extract energy from indigestible polysaccharides, decrease in the quantity of bacteria that are metabolically protective against obesity, altered hepatic lipogenesis and decrease in intestinal defence and immunity.⁵⁵ While well controlled animal studies support the role of antibiotics in the development of obesity, evidence from human studies are inconclusive. Epidemiological studies in healthy children have suggest-

ed that antibiotic usage in early life was associated with increased BMI and greater prevalence of obesity in healthy children, with the adverse events being more evident in males.⁵⁶ This sexual dimorphism may be due to the difference in adaptive response to diet, physical activity and physiological stress. Contradictorily, few studies did not observe any effect of antibiotics on weight gain in children.⁵⁷ More studies are therefore needed to establish and confirm the role of antibiotics in development of obesity in children.

GM and energy-dense, nutrient and fibre poor diets

The GM partially impacts the ability to extract and store calories from food. The GM composition could affect weight gain independent of calorie intake and other factors such as physical activity, use of proton pump inhibitors or antibiotics.⁵⁸ A low GM diversity is associated with higher weight gain over a period of time. High-fibre diet is positively associated with GM diversity and negatively associated with high weight gain. SCFAs, produced by fermentation of dietary fibre, have been known to improve insulin sensitivity and fatty acid oxidation (Figure 1).⁵⁸

Availability and consumption of energy-dense but fibre- and nutrient-poor foods have become exacerbated because of rural to urban migration, which is also responsible for the rise in obesity and diabetes outcomes in India with the transition from fibre-rich foods (in rural areas) to easily available calorie-dense, nutrient-poor foods (in urban areas).⁵⁹ Though not yet studied in a systematic manner, it is highly likely that such migration of already undernourished children is leading to GM dysbiosis-resultant inflammation altering their metabolism to an adiposity-prone mode.

CAN THE GM IMPROVE INFANT GROWTH AND REDUCE IIDBM?

Early childhood years is an important period for growth and development; any disturbances during this period can have short-term as well as long-term effects on health and development of the child.² Diet is one of the major causes of malnutrition. The GM is heavily influenced by the quality and composition of diet (fibre, fat, carbohydrates, proteins and vitamins).¹⁷ An apparent gut dysbiosis characterised by depletion of healthy bacteria has been noted in children with malnutrition.² Hence, modifying the GM in early life through dietary interventions to improve health and development of the child can be beneficial in the prevention of IIDBM (Figure 2).

Formula feeding (FF), attributable to limited oligosaccharides and high protein concentrations, causes changes in GM that are associated with OW/OB.⁶⁰ Early complementary feeding (CF) introduction, at or before 3 months, causes high gut diversity, alters GM composition at 3 and 12 months and increases faecal butyrate and total SCFA concentrations at 12 months.⁶¹ Hence early introduction of CF can lead to obesity and immune disorders through changes in GM and SCFA concentrations.

Brief supplementation of neonates with formula has been associated with decrease in *Bifidobacteriaceae* and increase in *Enterobacteriaceae* at 3 to 4 months. At 12

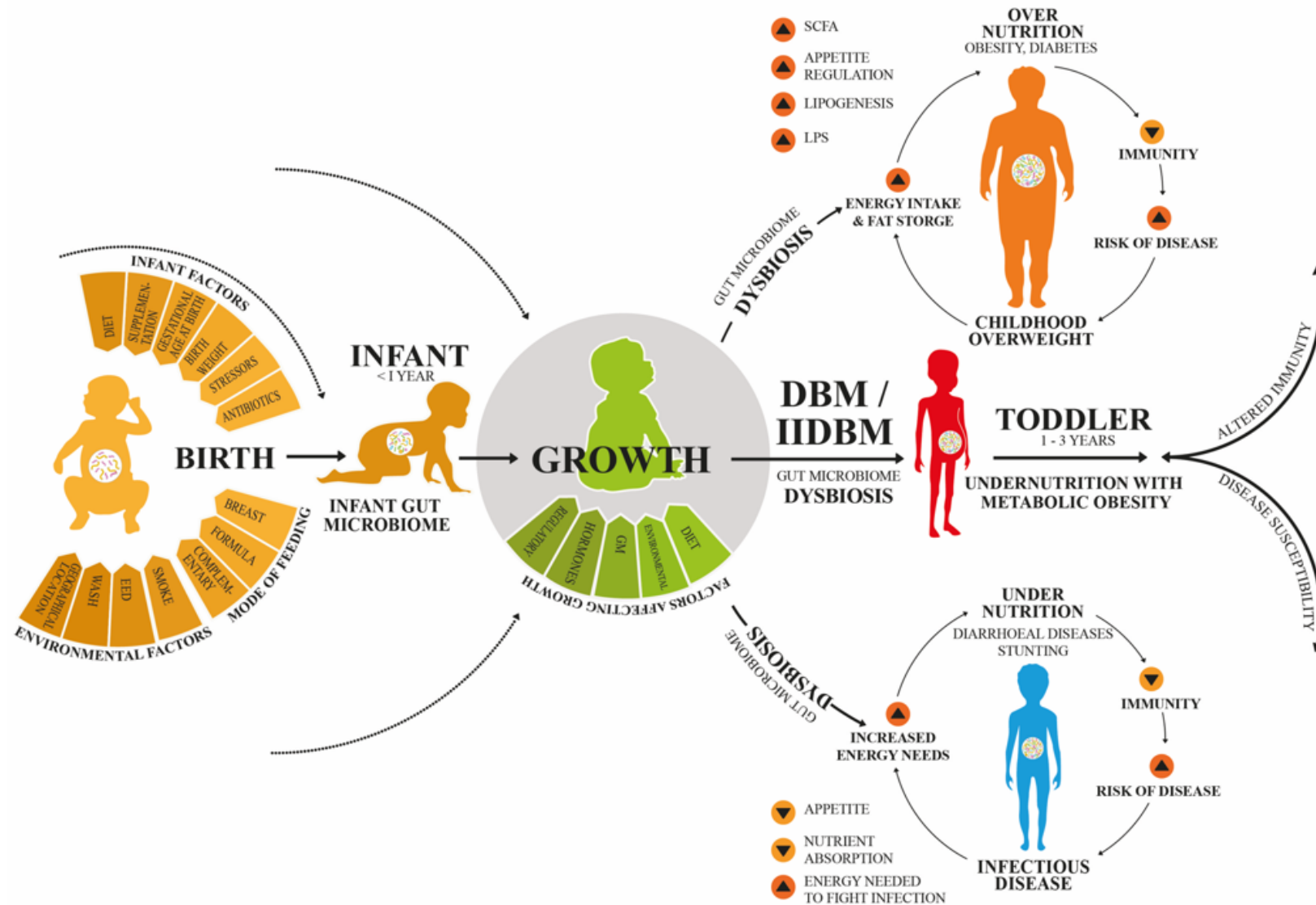


Figure 2. Summary of plausible factors that influence GM and growth. Solid line represents gut microbiome development and childhood growth, and dotted line represents the plausible interventions to improve gut microbiome. EED: Environmental enteric dysfunction; SCFA: Short-chain-fatty-acid; LPS: Lipopolysaccharide; WASH: Water sanitation and hygiene; IGM: Infant gut microbiome; GM: Gut microbiome; DBM: Double burden of malnutrition; IIDBM: Intra-individual double burden of malnutrition.

months, the GM profile differed according to type of feeding observed at 6 months of age; both partially breastfed and formula fed infants had profiles similar to non-breastfed infants while infants who had CF introduction without formula showed profiles similar to exclusive breastfed infants. This study observed that GM profiles at 3 months were more indicative of risk of overweight than GM profiles at 12 months and that FF is associated with OW/OB.⁶⁰

Antibiotic exposure in early life increases risk of childhood obesity and the GM may play a causal role in this. During the first month of life, antibiotic exposure is associated with a significant increase in BMI and body fat percentage in infants between 6 to 24 months of age.⁶² Environmental factors such as maternal smoking causes increase in Enterobacteriaceae in neonates; increase in *Lachnospiraceae*, *Bacteroides* and *Staphylococcus* at 6 months of age and an increase in *Firmicutes* and *Ruminococcus* at 3 months of age which can increase the risk of childhood OW/OB at 1 and 3 years of age.⁶³

Studies have supported the findings that breastfeeding is protective against overweight and that GM may contribute to this effect. A prospective birth cohort provided evidence that concentrations of SCFAs butyrate, formic acid, and acetate in human milk are negatively associated with infant adiposity and thus it provides early protection against excess weight gain.⁶⁴

Microbiota-directed complementary food (MDCF) studies have been shown to help children with undernutrition.⁶⁵ A randomised, double-blind controlled feeding study that observed effects of MDCFs in gnotobiotic animals and undernourished children identified a lead MDCF that changes the abundances of targeted bacteria and helps in growth and development in children with moderate acute malnutrition (MAM).⁶⁶ Another RCT that studied effects of a MDCF in children with MAM observed that MDCF was positively correlated with weight-for-length Z-score and the targeted modulation of GM by MDCF may be linked to growth.⁶⁵ Addition of common bean to complementary feed, in a study on rural African children where chronic malnutrition is pervasive, improved gut health.⁶⁷ The fibre from common bean may alter GM positively and reduce chronic inflammation thus improving gut health. A clinical trial in Nicaragua and Mali observed that dietary rice bran supplementation during infant weaning period, 6 to 12 months of age, modulated and supported metabolism by GM and improved growth outcomes.⁶⁸

Probiotic supplementation (*Lactobacillus rhamnosus GG* and *Bifidobacterium animalis subsp. lactis BB-12*) reduced cumulative incidence of diarrhoea in a RCT study involving Ugandan children with SAM.⁶⁹ In another RCT, probiotic supplementation had no effect on diarrhoea in children with SAM during the hospital stay; however, it reduced the number of diarrhoeal days by 26% in outpatient treatment.⁷⁰ No difference in weight gain was observed between the probiotic and placebo groups during the 8 to 12 weeks of treatment.⁷⁰

CONCLUSION

The increase in DBM and IIDBM globally over the years is a pressing public health concern. The GM and its me-

tabolites represent an important focus area here, and a better understanding of their role in host metabolism might help in preventing risk of obesity and supporting healthy infant growth. The effect of the GM response, to specific diets in children with malnutrition, needs further research to understand how dietary modification/intervention can influence GM, to optimise feeding strategies and to prevent undernutrition and overnutrition, while promoting healthy infant growth. Early differences in GM composition pave the way to the onset of childhood obesity; thus, early modification of GM to prevent later obesity can provide a novel preventive strategy to prevent long-term risk of NCDs.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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REFERENCES

1. World Health Organization. The Double Burden of Malnutrition. Policy brief. WHO/NMH/NHD/17.3. Geneva: WHO; 2017. [cited 2021/11/30]; Available from: <https://apps.who.int/iris/bitstream/handle/10665/255413/WHO-NMH-NHD-17.3-eng.pdf>.
2. Wells JC, Sawaya AL, Wibaek R, Mwangome M, Poullas MS, Yajnik CS, Demaio A. The double burden of malnutrition: aetiological pathways and consequences for health. *Lancet*. 2020;395:75-88. doi: 10.1016/S0140-6736(19)32472-9.
3. Bentham J, Di Cesare M, Bilano V, Bixby H, Zhou B, Stevens GA et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet*. 2017;390:2627-42. doi: 10.1016/S0140-6736(17)32129-3.
4. Ministry of Health and Family Welfare (MoHFW), Government of India, UNICEF and Population Council. Comprehensive National Nutrition Survey: 2016–2018. CNNS National Report. New Delhi; 2019. [cited 2021/11/30]; Available from: <https://nhm.gov.in/WriteReadData/1892s/1405796031571201348.pdf>.
5. Ministry of Health and Family Welfare (MoHFW), Government of India. National Family Health Survey (NFHS-5) 2019-21. NFHS; 2021. [cited 2021/11/30]; Available from: http://rchiips: nfhs/factsheet_NFHS-5.shtml
6. Sachdev HS, Porwal A, Sarna A, Acharya R, Ramesh S, Kapil U, Kurpad AV. Intraindividual double-burden of anthropometric undernutrition and “metabolic obesity” in Indian children: a paradox that needs action. *Eur J Clin Nutr*. 2021;75:1205-17. doi: 10.1038/s41430-021-00916-3.
7. Kurpad AV, Varadharajan KS, Aeberli I. The thin-fat phenotype and global metabolic disease risk. *Curr Opin Clin Nutr Metab Care*. 2011;14:542-7. doi: 10.1097/MCO.0b013e32834b6e5e.
8. World Health Organisation. Global Health Estimates: Life expectancy and leading causes of death and disability. WHO; 2019. [cited 2021/11/30]; Available from: www.who.int/data/gho/data/themes/mortality-and-global-health-estimates
9. Nguyen PH, Scott S, Headey D, Singh N, Tran LM, Menon P, Ruel MT. The double burden of malnutrition in India:

- Trends and inequalities (2006–2016). *PLoS One*. 2021;16:e0247856. doi: 10.1371/JOURNAL.PONE.0247856.
10. Waterlow JC. Childhood malnutrition in developing nations: looking back and looking forward. *Annu Rev Nutr*. 1994;14:1-20. doi: 10.1146/annurev.nu.14.070194.000245.
 11. Hoffman DJ, Sawaya AL, Verreschi I, Tucker KL, Roberts SB. Why are nutritionally stunted children at increased risk of obesity? Studies of metabolic rate and fat oxidation in shantytown children from São Paulo, Brazil. *Am J Clin Nutr*. 2000;72:702-70. doi: 10.1093/AJCN/72.3.702.
 12. Gevers D, Knight R, Petrosino JF, Huang K, McGuire AL, Birren BW, Nelson KE, White O, Methé BA, Huttenhower C. The Human Microbiome Project: A community resource for the healthy human microbiome. *PLoS Biol*. 2012;10:e1001377. doi: 10.1371/journal.pbio.1001377.
 13. Duvall C, Gibbons SM, Gurry T, Irizarry RA, Alm EJ. Meta-analysis of gut microbiome studies identifies disease-specific and shared responses. *Nat Commun*. 2017;8:1784. doi: 10.1038/S41467-017-01973-8.
 14. Subramanian S, Huq S, Yatsunenkov T, Haque R, Mahfuz M, Alam MA et al. Persistent gut microbiota immaturity in malnourished Bangladeshi children. *Nature*. 2014;510:417-21. doi: 10.1038/nature13421.
 15. Indiani CMDSP, Rizzardi KF, Castelo PM, Ferraz LFC, Darrieux M, Parisotto TM. Childhood obesity and Firmicutes/Bacteroidetes ratio in the gut microbiota: A systematic review. *Child Obes*. 2018;14:501-9. doi: 10.1089/chi.2018.0040.
 16. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. *PLoS Biol*. 2007;5:e177. doi: 10.1371/journal.pbio.0050177.
 17. Maher SE, O'Brien EC, Moore RL, Byrne DF, Geraghty AA, Saldova R, Murphy EF, Van Sinderen D, Cotter PD, McAuliffe FM. The association between the maternal diet and the maternal and infant gut microbiome: A systematic review. *Br J Nutr*. 2020;1-29. doi: 10.1017/S0007114520000847.
 18. Ho NT, Li F, Lee-Sarwar KA, Tun HM, Brown BP, Pannaraj PS et al. Meta-analysis of effects of exclusive breastfeeding on infant gut microbiota across populations. *Nat Commun*. 2018;9:4169. doi: 10.1038/S41467-018-06473-X.
 19. Ejtahed HS, Angoorani P, Soroush AR, Hasani-Ranjbar S, Siadat SD, Larijani B. Gut microbiota-derived metabolites in obesity: a systematic review. *Biosci Microbiota Food Health*. 2020;39:65-76. doi: 10.12938/BMFH.2019-026.
 20. Moreno-Navarrete JM, Fernandez-Real JM. The gut microbiota modulates both browning of white adipose tissue and the activity of brown adipose tissue. *Rev Endocr Metab Disord*. 2019;20:387-97. doi: 10.1007/S11154-019-09523-X.
 21. Riva A, Borgo F, Lassandro C, Verduci E, Morace G, Borghi E, Berry D. Pediatric obesity is associated with an altered gut microbiota and discordant shifts in Firmicutes populations. *Environ Microbiol*. 2017;19:95-105. doi: 10.1111/1462-2920.13463.
 22. Schwartz A, Taras D, Schäfer K, Beijer S, Bos NA, Donus C, Hardt PD. Microbiota and SCFA in lean and overweight healthy subjects. *Obesity*. 2010;18:190-5. doi: 10.1038/oby.2009.167.
 23. Lu Y, Fan C, Li P, Lu Y, Chang X, Qi K. Short chain fatty acids prevent high-fat-diet-induced obesity in mice by regulating G protein-coupled receptors and gut microbiota. *Sci Rep*. 2016;6:37589. doi: 10.1038/srep37589.
 24. Den Besten G, Bleeker A, Gerding A, Van Eunen K, Havinga R, Van Dijk TH et al. Short-chain fatty acids protect against high-fat diet-induced obesity via a PPAR γ -dependent switch from lipogenesis to fat oxidation. *Diabetes*. 2015;64:2398-408. doi: 10.2337/DB14-1213.
 25. Virtue AT, McCright SJ, Wright JM, Jimenez MT, Mowel WK, Kotzin JJ et al. The gut microbiota regulates white adipose tissue inflammation and obesity via a family of microRNAs. *Sci Transl Med*. 2019;11:eaav1892. doi: 10.1126/scitranslmed.aav1892.
 26. Schiattarella GG, Sannino A, Toscano E, Giugliano G, Gargiulo G, Franzone A, Trimarco B, Esposito G, Perrino C. Gut microbe-generated metabolite trimethylamine-N-oxide as cardiovascular risk biomarker: a systematic review and dose-response meta-analysis. *Eur Heart J*. 2017;38:2948-56. doi: 10.1093/eurheartj/ehx342.
 27. Barrea L, Annunziata G, Muscogiuri G, Di Somma C, Laudisio D, Maisto M, de Alteriis G, Tenore GC, Colao A, Savastano S. Trimethylamine-N-oxide (TMAO) as novel potential biomarker of early predictors of metabolic syndrome. *Nutrients*. 2018;10:1971. doi: 10.3390/NU10121971.
 28. Dehghan P, Farhangi MA, Nikniaz L, Nikniaz Z, Asghari-Jafarabadi M. Gut microbiota-derived metabolite trimethylamine N-oxide (TMAO) potentially increases the risk of obesity in adults: An exploratory systematic review and dose-response meta-analysis. *Obes Rev*. 2020;21:e12993. doi: 10.1111/OBR.12993.
 29. Farhangi MA, Vajdi M. Novel findings of the association between gut microbiota-derived metabolite trimethylamine N-oxide and inflammation: results from a systematic review and dose-response meta-analysis. *Crit Rev Food Sci Nutr*. 2020;60:2801-23. doi: 10.1080/10408398.2020.1770199.
 30. Geidl-Flueck B, Hochuli M, Németh Á, Eberl A, Derron N, Köfeler HC, Tappy L, Berneis K, Spinas GA, Gerber PA. Fructose- and sucrose- but not glucose-sweetened beverages promote hepatic de novo lipogenesis: A randomized controlled trial. *J Hepatol*. 2021;75:46-54. doi: 10.1016/j.jhep.2021.02.027.
 31. Softic S, Meyer JG, Wang GX, Gupta MK, Batista TM, Lauritzen HPMM et al. Dietary sugars alter hepatic fatty acid oxidation via transcriptional and post-translational modifications of mitochondrial proteins. *Cell Metab*. 2019;30:735-53.e4. doi: 10.1016/J.CMET.2019.09.003.
 32. Todoric J, Di Caro G, Reibe S, Henstridge DC, Green CR, Vrbancac A et al. Fructose stimulated de novo lipogenesis is promoted by inflammation. *Nat Metab*. 2020;2:1034-45. doi: 10.1038/s42255-020-0261-2.
 33. Chakaroun R, Massier L, Kovacs P. Gut microbiome, intestinal permeability, and tissue bacteria in metabolic disease: perpetrators or bystanders? *Nutrients*. 2020;12:1082. doi: 10.3390/nu12041082.
 34. Ferguson JF, Mulvey CK, Patel PN, Shah RY, Doveikis J, Zhang W et al. Omega-3 PUFA supplementation and the response to evoked endotoxemia in healthy volunteers. *Mol Nutr Food Res*. 2014;58:601-13. doi: 10.1002/mnfr.201300368.
 35. Araya J, Rodrigo R, Videla LA, Thielemann L, Orellana M, Pettinelli P, Poniachik J. Increase in long-chain polyunsaturated fatty acid n - 6/n - 3 ratio in relation to hepatic steatosis in patients with non-alcoholic fatty liver disease. *Clin Sci (Lond)*. 2004;106:635-43. doi: 10.1042/CS20030326.
 36. Nobili V, Bedogni G, Alisi A, Pietrobattista A, Risé P, Galli C, Agostoni C. Docosahexaenoic acid supplementation decreases liver fat content in children with non-alcoholic fatty liver disease: double-blind randomised controlled clinical trial. *Arch Dis Child*. 2011;96:350-3. doi: 10.1136/ADC.2010.192401.

37. Boyraz M, Pirgon Ö, Dündar B, Çekmez F, Hatipoğlu N. Long-term treatment with n-3 polyunsaturated fatty acids as a monotherapy in children with nonalcoholic fatty liver disease. *J Clin Res Pediatr Endocrinol.* 2015;7:121-7. doi: 10.4274/JCRPE.1749.
38. Jones JJ, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. *Endocr Rev.* 1995;16:3-34. doi: 10.1210/EDRV-16-1-3.
39. Arturi F, Succurro E, Procopio C, Pedace E, Mannino GC, Lugarà M et al. Nonalcoholic fatty liver disease is associated with low circulating levels of insulin-like growth factor-I. *J Clin Endocrinol Metab.* 2011;96:E1640-4. doi: 10.1210/JC.2011-1227.
40. Liang S, Cheng X, Hu Y, Song R, Li G. Insulin-like growth factor I and metabolic parameters are associated with nonalcoholic fatty liver disease in obese children and adolescents. *Acta Paediatr.* 2017;106:298-303. doi: 10.1111/APA.13685.
41. Dogra S, Sakwinska O, Soh S-E, Ngom-Bru C, Brück WM, Berger B et al. Dynamics of infant gut microbiota are influenced by delivery mode and gestational duration and are associated with subsequent adiposity. *mBio.* 2015;6:e02419-14. doi: 10.1128/MBIO.02419-14.
42. Kalliomäki M, Collado MC, Salminen S, Isolauri E. Early differences in fecal microbiota composition in children may predict overweight. *Am J Clin Nutr.* 2008;87:534-8. doi: 10.1093/ajcn/87.3.534.
43. Stanislawski MA, Dabelea D, Wagner BD, Iszatt N, Dahl C, Sontag MK, Knight R, Lozupone CA, Eggesbø M. Gut Microbiota in the first 2 years of life and the association with body mass index at age 12 in a Norwegian Birth Cohort. *mBio.* 2018;9:e01751-18. doi: 10.1128/MBIO.01751-18.
44. Tseng CH, Wu CY. The gut microbiome in obesity. *J Formos Med Assoc.* 2019;118:S3-9. doi: 10.1016/j.jfma.2018.07.009.
45. Vael C, Verhulst SL, Nelen V, Goossens H, Desager KN. Intestinal microflora and body mass index during the first three years of life: an observational study. *Gut Pathog.* 2011;3:8. doi: 10.1186/1757-4749-3-8.
46. Grander C, Grabherr F, Moschen AR, Tilg H. Non-alcoholic fatty liver disease: cause or effect of metabolic syndrome. *Visc Med.* 2016;32:329-34. doi: 10.1159/000448940.
47. Harper KM, Mutasa M, Prendergast AJ, Humphrey J, Manges AR. Environmental enteric dysfunction pathways and child stunting: A systematic review. *PLoS Negl Trop Dis.* 2018;12:e0006205. doi: 10.1371/journal.pntd.0006205.
48. Araújo JR, Tomas J, Brenner C, Sansonetti PJ. Impact of high-fat diet on the intestinal microbiota and small intestinal physiology before and after the onset of obesity. *Biochimie.* 2017;141:97-106. doi: 10.1016/J.BIOCHI.2017.05.019.
49. Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. From the cover: mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc Natl Acad Sci U S A.* 2007;104:979-84. doi: 10.1073/PNAS.0605374104.
50. Ehrlich AM, Pacheco AR, Henrick BM, Taft D, Xu G, Huda MN et al. Indole-3-lactic acid associated with Bifidobacterium-dominated microbiota significantly decreases inflammation in intestinal epithelial cells. *BMC Microbiol.* 2020;20. doi: 10.1186/s12866-020-02023-y.
51. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci.* 2012;13:701-12. doi: 10.1038/NRN3346.
52. Alcock J, Maley CC, Aktipis CA. Is eating behavior manipulated by the gastrointestinal microbiota? Evolutionary pressures and potential mechanisms. *Bioessays.* 2014;36:940-9. doi: 10.1002/BIES.201400071.
53. Fetissov SO. Role of the gut microbiota in host appetite control: bacterial growth to animal feeding behaviour. *Nat Rev Endocrinol.* 2017;13:11-25. doi: 10.1038/nrendo.2016.150.
54. Cho I, Yamanishi S, Cox L, Methé BA, Zavadil J, Li K et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature.* 2012;488:621-6. doi: 10.1038/NATURE11400.
55. Cox LM, Blaser MJ. Antibiotics in early life and obesity. *Nat Rev Endocrinol.* 2015;11:182-90. doi: 10.1038/NRENDO.2014.210.
56. Azad MB, Bridgman SL, Becker AB, Kozyrskyj AL. Infant antibiotic exposure and the development of childhood overweight and central adiposity. *Int J Obes (Lond).* 2014;38:1290-8. doi: 10.1038/IJO.2014.119.
57. Edmonson MB, Eickhoff JC. Weight gain and obesity in infants and young children exposed to prolonged antibiotic prophylaxis. *JAMA Pediatr.* 2017;171:150-6. doi: 10.1001/JAMAPEDIATRICS.2016.3349.
58. Menni C, Jackson MA, Pallister T, Steves CJ, Spector TD, Valdes AM. Gut microbiome diversity and high-fibre intake are related to lower long-term weight gain. *Int J Obes (Lond).* 2017;41:1099-1105. doi: 10.1038/IJO.2017.66.
59. Ebrahim S, Kinra S, Bowen L, Andersen E, Ben-Shlomo Y, Lyngdoh T et al. The effect of rural-to-urban migration on obesity and diabetes in India: a cross-sectional study. *PLoS Med.* 2010;7:e1000268. doi: 10.1371/journal.pmed.1000268.
60. Forbes JD, Azad MB, Vehling L, Tun HM, Konya TB, Guttman DS et al. Association of exposure to formula in the hospital and subsequent infant feeding practices with gut microbiota and risk of overweight in the first year of life. *JAMA Pediatr.* 2018;172:e181161. doi: 10.1001/jamapediatrics.2018.1161.
61. Differding MK, Benjamin-Neelon SE, Hoyo C, Østbye T, Mueller NT. Timing of complementary feeding is associated with gut microbiota diversity and composition and short chain fatty acid concentrations over the first year of life. *BMC Microbiol.* 2020;20:56. doi: 10.1186/s12866-020-01723-9.
62. Smith-Brown P, Morrison M, Krause L, Davies PSW. Microbiota and body composition during the period of complementary feeding. *J Pediatr Gastroenterol Nutr.* 2019;69:726-32. doi: 10.1097/MPG.0000000000002490.
63. McLean C, Jun S, Kozyrskyj A. Impact of maternal smoking on the infant gut microbiota and its association with child overweight: a scoping review. *World J Pediatr.* 2019;15:341-9. doi: 10.1007/s12519-019-00278-8.
64. Prentice PM, Schoemaker MH, Vervoort J, Hettinga K, Lambers TT, Van Tol EAF et al. Human milk short-chain fatty acid composition is associated with adiposity outcomes in infants. *J Nutr.* 2019;149:716-22. doi: 10.1093/jn/nxy320.
65. Chen RY, Mostafa I, Hibberd MC, Das S, Mahfuz M, Naila NN et al. A Microbiota-directed food intervention for undernourished children. *N Engl J Med.* 2021;384:1517-28. doi: 10.1056/NEJMJA2023294.
66. Gehrig JL, Venkatesh S, Chang HW, Hibberd MC, Kung VL, Cheng J et al. Effects of microbiota-directed foods in gnotobiotic animals and undernourished children. *Science.* 2019;365:eaau4732. doi: 10.1126/science.aau4732.
67. Agapova SE, Stephenson KB, Divala O, Kaimila Y, Maleta KM, Thakwalakwa C, Isabel Ordiz M, Trehan I, Manary MJ. Additional common bean in the diet of Malawian children does not affect linear growth, but reduces intestinal permeability. *J Nutr.* 2018;148:267-74. doi: 10.1093/jn/nxx013.

68. Zambrana LE, McKeen S, Ibrahim H, Zarei I, Borresen EC, Doumbia L et al. Rice bran supplementation modulates growth, microbiota and metabolome in weaning infants: a clinical trial in Nicaragua and Mali. *Sci Rep.* 2019;9:13919. doi: 10.1038/s41598-019-50344-4.
69. Castro-Mejía JL, O’Ferrall S, Krych Ł, O’Mahony E, Namusoke H, Lanyero B et al. Restitution of gut microbiota in Ugandan children administered with probiotics (*Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. *lactis* BB-12) during treatment for severe acute malnutrition. *Gut Microbes.* 2020;11:855-67. doi: 10.1080/19490976.2020.1712982.
70. Grenov B, Namusoke H, Lanyero B, Nabukeera-Barungi N, Ritz C, Mølgaard C, Friis H, Michaelsen KF. Effect of probiotics on diarrhea in children with severe acute malnutrition: a randomized controlled study in Uganda. *J Pediatr Gastroenterol Nutr.* 2017;64:396-403. doi: 10.1097/MPG.000000000000015