SEEJPH Volume XXVI, S2, 2025, ISSN: 2197-5248; Posted:03-02-2025

Role of Gut Microbial Dysbiosis, Subsequent Metabolite Secretion, and Signalling Pathways Focusing on Gut - Brain Axis and Pro-Inflammatory Cytokine Secretion in Infection - Constipation or Diarrhoea as the Initial Presenting Symptom - A Systematic Review and Meta - Analysis

Krithikaa Sekar [1*], S.S.M. Uma Mageswari [2]

[1] *Department of Microbiology, Vels Medical College and Hospital, Thiruvallur, Tamil Nadu, India.*
Email: krithikaasekar@yahoo.in
[2] *Department of Microbiology, Vels Medical College and Hospital, Thiruvallur, Tamil Nadu, India*
**Corresponding Author: Krithikaa Sekar*

KEYWORDS
Gut microbiota, dysbiosis, metagenomics, metabolomics, proteomics, gut-brain axis, cytokines, interleukins, metagenomics, metabolomics, proteomics.

ABSTRACT
The indigenous gut microbiota plays an important role in the maintenance of gut homeostasis. Dysbiosis, leading to the disruption of gut and overall homeostasis, leads to GI manifestations that hold key implications from One health perspective also. Here, we conducted a systematic review and meta-analysis of 35 horizontal studies investigating the association between gut microbiota, metabolites and signalling pathways and symptoms. In constipation, we observed correlation between increased fecal short chain fatty acids with *Coprococcus, Fecalobacterium* and *Roseburia*, increased ghrelin with H.pylori, increased methane with *Methanobrevibacter* and *Methanogens* and increased serotonin with *Candida* species. In diarrhoea, we observed correlation between increased fecal bile acids with increased *Clostridia*, decreased *Blautia, Ruminococcaceae*, increased *Zonulin* with *E.coli* and other *Enterobactericiae*, increased calprotectin with increased *Hemophilus, Veillonella*, decreased *Clostridia*, increased RA factor and *Prevotella copri*, increased purine/uric acid with *Shigella* and *Enterococcus*, increased leptin associated with *E.histolytica* and *Strongyloides* increased TNF-alpha, IL6, CRP and decreased IL10 with all pathobionts and increased Acetylcholine with *B.subtilis* rather than *E.coli* or *S.aureus*. Our study highlights the significance of gut microbial dysbiosis in infection-associated constipation or diarrhoea. It also emphasizes the need for multi-omics studies to overcome the shortcomings of the existing GI pathogen and GI microbiome panels. Additional longitudinal and interventional studies are warranted to develop additional diagnostic tools and novel therapeutic interventions for a holistic approach to maintain gut health and overall well-being.

1. Background

Gut microbiota is composed of approximately 2172 bacterial species (*Firmicutes, Bacteroides, Proteobacteria and Actinomycetes*-98% approximately), helps maintaining gut homeostasis and various physiological processes like digestion and nutrient absorption, immune system modulation preventing infections and autoimmune disorders, hormone and neurotransmitter production that regulate appetite, mood, and cognitive function, gut barrier function preventing the passage of toxins and undigested food particles by maintaining gut epithelial integrity and regulating inflammation through the secretion of pro-inflammatory and anti-inflammatory cytokines. A healthy microbiome is characterized by Diversity, Stability and Resilience. Once microbial configuration is shifted, dysbiosis persists as a stable state and can assume various compositional manifestations depending on the trigger. So microbial community can be viewed as a conceptual energy landscape in which both health and dysbiotic state exist in different configuration, but the transition requires external force that are stronger than the stability of the system. Moreover, microbiome can adapt quickly to environmental changes due to its short generation times and microbiome can change faster than the human genome. The gut dysbiosis leads to changes in metabolite secretion and subsequent proinflammatory cytokine secretion and modulation in gut brain axis, thus being a major player in the development of morbidities like Irritable Bowel Syndrome, atherosclerosis, Parkinson's disease, obesity and type 2 diabetes, ankylosing spondylitis and unexplained miscarriage. Apart from morbidities, it also leads to work absenteeism, loss of productivity and negative impact on the quality of life. The diagnosis of dysbiosis

is also difficult as it is attributable to symptoms like diarrhoea or constipation, cultural differences in self-reporting of symptoms, access to healthcare or diagnostic services and health-seeking behavior. The diagnosis is also difficult because Koch's postulates is not applicable because of mutualism, blooming pathobionts and bystander effect. The existing GI infectious diseases panel or GI microbiome panel also has an incomplete coverage. Hence multi-omics based approaches are required for a broader analysis, functional insights into the metabolic pathways and microbial activities beyond species identification, discovery potential to identify new species and unknown genes having human disease association and personalized microbiome analysis for tailored interventions and personalized healthcare approaches. There is also inter-individual variability in taxonomic microbiota composition between healthy individuals as per demographic and socio-behavioural changes. There is also a de-novo theory of dysbiosis in which the microbial quantity changes is sufficient to cause the disease. This is also important from the One health perspective as it has a potential for zoonotic transmission, gut-environmental interface, therefore development and spread of anti-microbial resistance. Various methods are employed to study the pathophysiology and microbiology of dysbiosis including conventional culture methods, metagenomics, metabolomics and proteomics. Still, the concept of gut dysbiosis is complex and elusive of conclusion despite decades of research. Hence, this systematic review and meta-analysis aims to map gut microbial alterations, metabolite secretion and signalling pathways to constipation or diarrhoea as presenting symptoms of gut microbial dysbiosis and infection so as to develop novel diagnostic algorithms, diagnostic tools and therapeutic strategies to maintain the gut health and overall well-being in this era of urbanization and life-style and dietary alterations.

2. Materials and Methods

We conducted literature search on major databases like PubMed, Scopus, Web of Science and Cochrane library from 2014-2024, using the MeSH search terms- "gut dysbiosis", "metabolite", "constipation", "diarrhoea", "gut-brain axis", "pro-inflammatory cytokines", "cross-sectional" and "case-control studies". Studies were included if they satisfied the above-mentioned criteria and excluded if they were not in English, review articles, abstracts or cohort studies or trials. A total of 60 studies (conventional methods-9, metagenomics-29, metabolomics-13, proteomics-9) were identified by the database, downloaded and screened for relevance and inclusion criteria. After screening, a total of 35 relevant articles with 1208 eligible participants were finalized for analysis after the extraction of data into Microsoft Excel spreadsheet. The PRISMA flowchart for data extraction is given below.

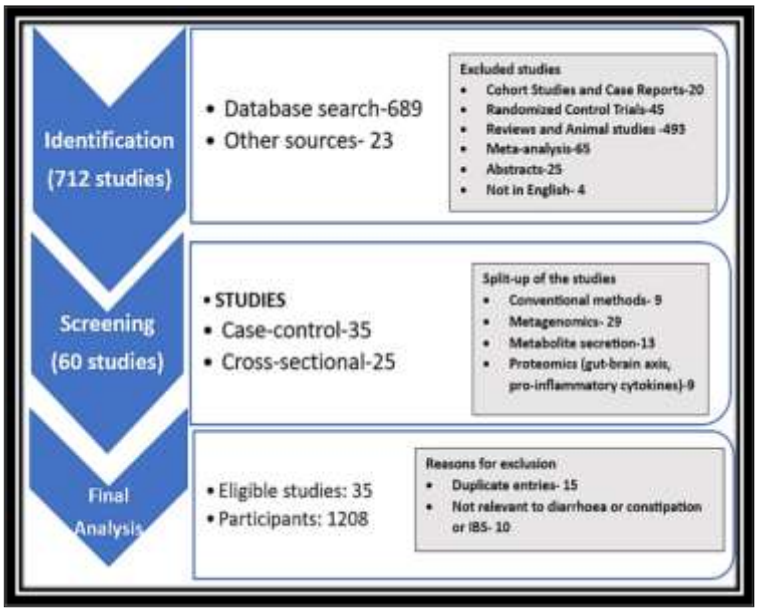

Figure 1: PRISMA Flowchart for study Selection

3. Results

The Forest Plot of the selected studies used for analysis revealed a pooled Odds ratio of 1.32 with a 95% Confidence Interval ranging from 1.17-1.49. The test for heterogeneity revealed a moderate variability among the studies (I^2=45%, p=0.04). The pooled Z score was 4.21 (p value <0.001) which indicates statistical significance.

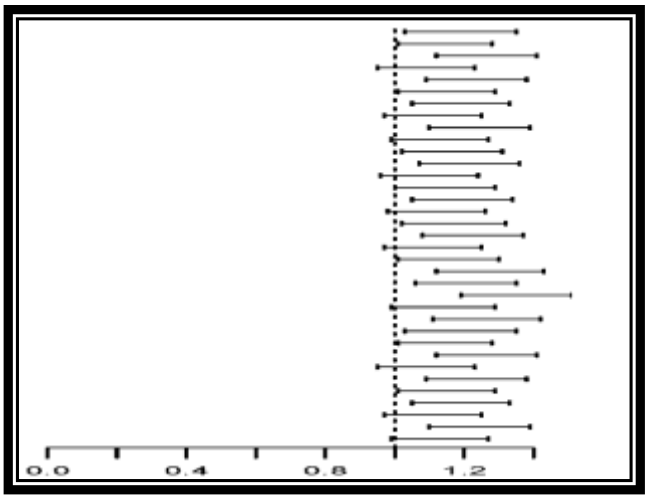

Figure 2: Forest Plot

Analysis on the diversity of the microbial flora and the variations in quantity of different taxonomic groups among the symptoms ie diarrhoea and constipation revealed that in constipation, there was a 33.58% decrease in *Bifidobacterium*, 28.23% decrease in *Faecalobacterium*, 43.58% increase in *Methanobrevibacter*, 54.35% increase in *H.pylori* and 18.25% increase in *Candida* species. In diarrhoea, there was 32.86% decrease in *Ruminococcaceae*, 18.92% decrease in *Blautia*, 16.65% decrease in *Lactobacillus*, 28.26% increase in *E.coli* and all other *Enterobactericiae*, 32.57% increase in *S.aureus*, 26.78% increase in *Clostridium* and 18.75% increase in *Candida* species. The same is pictorially represented in the bar chart provided below. In general, there was a reduction in diversity of microbial flora observed in patients presenting with symptoms.

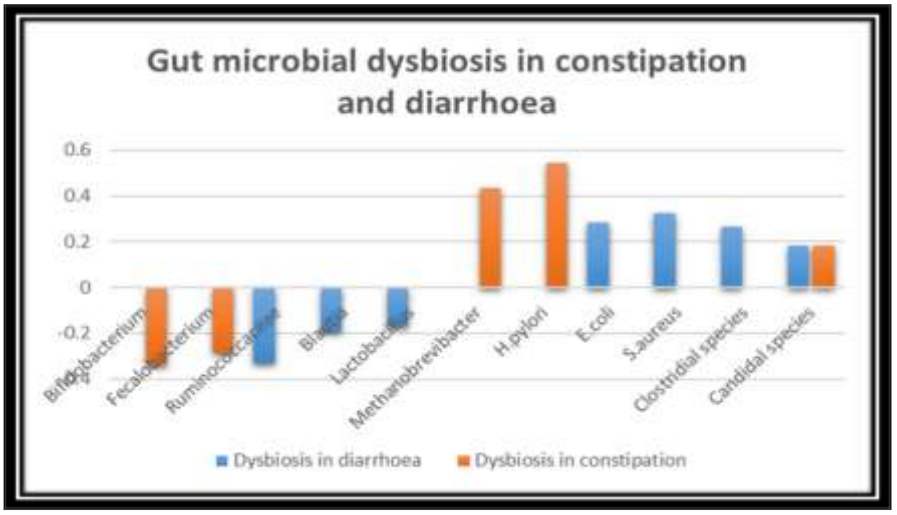

Figure 3: Pattern of microbial dysbiosis

Analysis on the association between the microbial diversity, metabolite secretion as indicated by metabolites and biomarkers and interleukin levels indicative of gut-brain axis dysbiosis and cytokine secretion alterations were measured using regression analysis against the symptoms-constipation and

diarrhoea and the following findings were revealed as provided in the surface plot below. The levels at which the particular organism was capable of creating metabolite, biomarker and interleukin alterations in patients suffering from diarrhoea and constipation vs the normal levels in healthy controls were also analyzed.

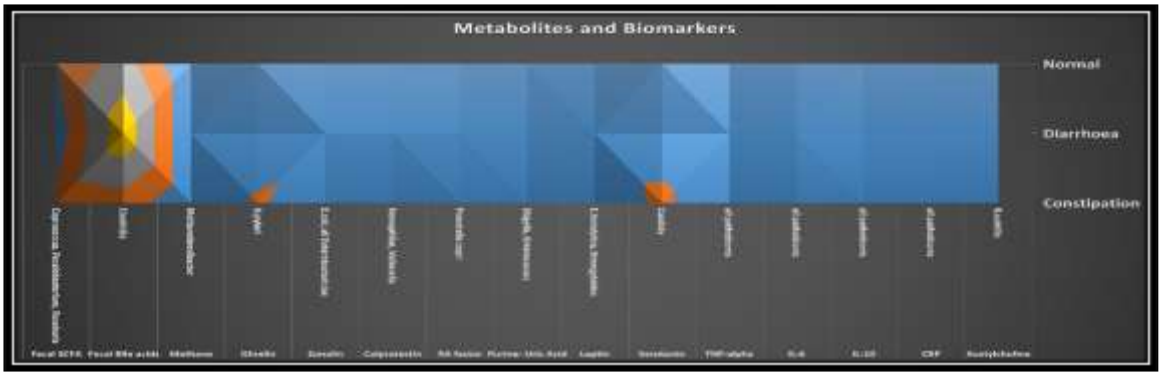

Figure 4: Integrative analysis of gut microbial dysbiosis, associated metabolites, biomarkers and symptoms

In constipation, we observed correlation between increased fecal short chain fatty acids (180 mmol/Kg) with *Coprococcus, Fecalobacterium* and *Roseburia*, increased ghrelin (150 fmol/mL) with H.pylori, increased methane (20 ppm) with *Methanobrevibacter* and *Methanogens* and increased serotonin (126.82 ng/mL) with *Candida* species. In diarrhoea, we observed correlation between increased fecal bile acids (160 mg/day) with increased *Clostridia*, decreased *Blautia, Ruminococcaceae*, increased *Zonulin* (20 ng/mL) with *E.coli* and other *Enterobactericiae*, increased calprotectin (20 Ug/mL) with increased *Hemophilus, Veillonella*, decreased *Clostridia*, increased RA factor (25 IU/mL) and *Prevotella copri*, increased purine/uric acid (10.3 mg/dL) with *Shigella* and *Enterococcus*, increased leptin (70 ng/mL) associated with *E.histolytica* and *Strongyloides* increased TNF-alpha (113.4 pg/mL), IL6 (11.3 pg/mL), CRP (48 mg/dL) and decreased IL10 (4.6 pg/mL) with all pathobionts and increased Acetylcholine (0.92 nmol/L) with *B.subtilis* rather than *E.coli* or *S.aureus*.

4. Discussion

Gut dysbiosis may be defined as the imbalance in the gut microbial equilibrium due to imbalance in the flora itself or changes in their functional composition along with metabolic activities and overall dysfunction in homeostasis. This may be due to bloom of pathobionts associated with inflammation induced remodeling of the intestinal ecosystem, loss of commensals combined with metabolite secretion that can impact the microglial function, epithelial tight junction barrier through TNF-alpha regulated by ERK 1/2 and Elk-1, reduction in alpha diversity caused by diet, xenobiotics and lifestyle changes. There are numerous theories suggesting the origin of dysbiosis. The first thought is that infection and inflammation cause deficiency of IL-10 that releases nutrients due to use of metal ions, inter-microbial competition, horizontal gene transfer, exploitation of antimicrobial peptides and products of aerobic and anaerobic cell respiration. Dysbiosis and genetics have a complex interplay- eg: *Bifidobacterium* is associated with host gene for lactase, vitamin D receptor and immune modulation are related, *Chistensenellaceae* and low BMI are associated. There is also an incidental spurious origin of dysbiosis theory in which neonatal intestinal colonization is influenced by the maternal microbiota and transmitted across generations and environmental transmission plays a role during development into adult life. The concept of One Health is important in this context as it has a potential for zoonotic transmission, gut-environmental interface, therefore development and spread of anti-microbial resistance.

Gut dysbiosis, immunity and metabolites:

Gut associated lymphoid tissue (GALT) constitutes 70% of the body's immune system. Microbial sensing through germline encoded PRRs influence microbial colonization eg: deficiency in TLR5 leads to loss of MYD88 signalling leading to microbial alterations resulting in hyperphagia and metabolic syndrome. Other PRRs may be related to NLR1 which recognize peptidoglycan layer of Gram-negative bacteria that leads to increase in commensals like *Bacteroides, Firmicutes* and *Actinomycetes*. Some NLR proteins combine to form inflammasomes leading to the activation of caspases and secretion of interleukins like IL-1, IL-6, Il-18, IL-15, IL-22 that change the innate lymphoid cells and expand Th1 and Th17 cells.eg: Intestinal Paneth cells secrete antimicrobial lectin Reg IIIy targeting Gram positive bacteria, IL-22 results in expansion of segmented filamentous bacterial population and TNF-alpha is associated with *H.typhlonius*. S-IgA targets lipopolysaccharide layer and thus increases the colonization by commensals. It is further influenced by follicular Th cells that secrete PD1 proteins and its deficiency may result in reduced *Bifidobacterium, Sutterella* and increased *Enterobactericiae*.

Metabolites play an important role in building up the communication between microbiome and immune system eg: tryptophan and ILCs, SCFA and Treg cells, *Mucispirillum* and S-IgA, decreased butyrate levels in irritable bowel syndrome and Coeliac Disease, RA factor and *Prevotella copri* that is the highest in Indian population. The pathogenesis of Rheumatoid arthritis attributed to *P.copri* may be due to deviation in metagenomic functions including metal ion metabolism, redox function and arginine metabolism. Methane, which is associated with M.smithii (marker of bacterial vaginosis), increases the ileal and colon transit time and raises the amplitude of contraction, slowing peristalsis and thereby causing constipation.

Microbiota contributes to the instigation of autoimmunity. Eg: loss of bacterial diversity precedes the symptom onset of Type 1 Diabetes but it is diagnosed only after seroconversion of patients. Loss of bacterial diversity is also associated with asthma caused by reduced levels of faecal acetate thereby inducing IgE secretion instead of IgA. Multiple sclerosis is due to the auto-reactivation of CD4+ T cells.

Gut-brain axis:

GBA is a complex cross-talk among gut-microbiota, intestinal epithelial cells, ENS, ANS, immune system and HPA. The intestinal epithelial cells are composed of various types of cells such as enterocytes, goblet cells, entero-endocrine cell, Paneth cells, stem cells and M cells along with tight junctional cells. Adherens junctions are the protein complexes that help maintain the integrity of the epithelial layer. The mucus layer is a protective barrier that covers the epithelial surface, preventing the entry of pathogens and toxins. The glycocalyx is a layer of carbohydrate molecules that covers the epithelial surface, helping to regulate the passage of molecules, gut integrity, gut homeostasis and restore the imbalance due to pathological insults. The disturbance in any one of the factors may lead to local and systemic inflammation, antigenic mimicry as in the case of T1D. Fecal SCFA help to restore mucosal barrier function after injury and administration of glutamine can prevent the disruption of tight junctions. Excess SCFA is associated with constipation, hence, the beneficial or adverse influence of SCFA on gut motility and thereby chronic diseases association is a matter of concern, for which further analysis is required. Serotonin, which is an important molecule of GBA, playing a crucial role in the development and function of CNS and ENS is mainly (around 95%) found in the gut (ENS) and very minimal quantity is seen in CNS (3%). Therefore, ENS comprising of more than 500 million neurons organized into complex micro-circuits may be considered as the second brain. The microbiota interact with GBA through vagus nerve with the help of neuropod cells, neuroendocrine signalling, interference with tryptophan metabolism, immune system, altered intestinal permeability and production of metabolites that are carried to the CNS across BBB. GBA can thereby alter mood and

behaviour, causing depression like symptoms, if serotonin in secreted in excess as seen patients suffering from constipation. Acetylcholine is a neurotransmitter that is involved in the cholinergic system. It regulates brain circuits associated with learning, memory and movement and its is affected by GBA1 mutation as seen in Parkinson's and other chronic neuro-degenerative diseases associated with constipation. In Parkinson's disease, there is chronic constipation and it precedes the development of motor symptoms by years, hence microbiome-based diagnostics can be used a screening test for early diagnosis. Similarly, elevated levels of serotonin is seen in autistic individuals and appropriate therapy may be provided to alleviate the symptoms and improve cognitive function.

Use of Multi-omics technologies in gut microbiome studies:

The gut microbiota is composed of both culturable and unculturable micro-organisms that interact with each other and also with the host. The presence or absence of a microbe does not indicate the presence of a disease and deeper analysis regarding the phylogeny, metabolic potential and pathways and secretion of actual proteins and metabolites are required for ascertaining causality. The existing GI infectious diseases panel or GI microbiome panel also has an incomplete coverage. Metagenomics sequences the genomes of microbes through gene marker analysis and shotgun sequencing. This is mainly performed to analyse the microbiota and their varying proportions. Horizontal gene transfer may occur among the microbes which may create difficulty in analysing the diversity. There are also challenges in mapping of the genomes of unidentified microbes. Hence, applying sole metagenomics may provide a prediction about the potential functions of microbes, but further comprehensive analysis is required. Meta-proteomics applies mass spectrometry to analyse and measure the level of expressed proteins. But it may be influenced by the host proteins and undigested food particles. Combination of metagenomics with metabolomics and meta-proteomics may be employed to overcome this issue. Metabolomics is the study of metabolites in a given sample at a particular time. In targeted metabolomics, specific metabolites linked to the pathways are analysed, whereas in untargeted approach all metabolites linked to the specific pathways for the diseases are analysed. It has been used mainly to detect biomarkers. It is futile to use metabolomics only in the analysis as many microbes may produce the same metabolite. Hence multi-omics-based approaches are required for a broader analysis, functional insights into the metabolic pathways and microbial activities beyond species identification, discovery potential to identify new species and unknown genes having human disease association and personalized microbiome analysis for tailored interventions and personalized healthcare approaches.

Confounding Factors and gut microbial dysbiosis association with various diseases:

Horizontal studies have a limited capacity to identify the host microbial dysbiosis and pathology of diseases. These may be associated with the risk of false positives due to inter-individual heterogeneity and population-wide differences in age, lifestyle and self-reporting of symptoms. There is a need for matching of the study population in terms of lifestyle, diet and frequency of bowel movements. There are several published studies that suggest the association of gut microbial diversity with socio-demographic factors, occupational factors, pre-existing co-morbidities and genetic disorders. Furthermore, this matching is anticipated to increase robustness and reproducibility in resolving the complexities associated with determining the causality of the disease with microbial dysbiosis. There is also variation in the microbial flora between the different sections of the gut namely oral flora, stomach, small intestine and colonic flora. There is also a need to consider these microbial interactions with each other and their mechanisms of survival and disease causation. Hence, longitudinal studies are required to analyse how we can leverage all the possible confounding factors with disease causation in gut microbial dysbiosis.

Possible therapeutic options:

Various therapeutic strategies have been developed to restore gut microbial homeostasis. Antibiotics like vancomycin, fidaxomicin, rifaximin, metronidazole can be used to treat gut dysbiosis with *Cl.difficile*, SIBO, IBD etc. as an active strategy. Conversely, existing gut microbial flora like *Bifidobacterium* producing bifidin and bifilactone, *Lactobacillus* producing lactacin and acidolin, *Streptomyces* producing streptomycin and tetracycline, *Bacillus* producing bacitracin and polymyxin, *Paenibacillus* producing polymyxin and colistin may be introduced as a passive strategy. The above-mentioned therapeutic strategies may be used as probiotics or used in combination with other molecules like inulin, oligofructose etc as synbiotics which needs to be tailor-made according to the patient's gut requirement. Bacteriophages can be engineered to produce anti-microbial peptides. These bacteriophages can be conjugated with nano-biotics and these can be used to control pathogen population and restore gut homeostasis. Faecal microbiota transplantation is another therapeutic strategy that still needs to be explored due to its operational and regulatory challenges and the colonization by antibiotic resistant bacteria. Lifestyle modifications such as dietary changes and stress management options are also available.

Acknowledgment:

We would like to thank the VMCH management for providing with an opportunity to publish this article

Conflict of Interest Statement:

The authors have no financial, professional or personal interest that could have influenced the design or conduct of this systematic review and meta-analysis

Contribution:

Krithikaa Sekar- Conceptualization, drafting the manuscript and data analysis

S.S.M.Uma Mageswari- Drafting the Manuscript and Administrative support

5. Conclusion

Our study attempted to map gut microbiota, metabolite secretion, and signaling pathways to various diseases, but had limitations including variability in analytical techniques, confounding demographic factors, and lack of longitudinal design to establish causality. Future studies should address these limitations through longitudinal and interventional designs, standardized methods, and consideration of confounding factors. Targeted diagnostic solutions are needed to understand and characterize the microbiome, visualize interactions with metabolites, and elucidate microbe mediation of infectious diseases, immune-oncology, and immunology of chronic diseases. Ultimately, research should focus on developing personalized therapeutic interventions, diagnostic tools, and algorithms to promote gut health and overall well-being.

References:

[1] Belkova, N., Klimenko, E., Romanitsa, A., Pogodina, A., and Rychkova, L. (2020). Metagenomic 16S rDNA amplicon datasets from adolescents with normal weight, obesity, and obesity with irritable bowel syndrome from eastern Siberia, Russia. *Data Brief* 32:106141:106141. doi: 10.1016/j.dib.2020.106141

[2] Chassard, C., Dapoigny, M., Scott, K. P., Crouzet, L., Del'homme, C., Marquet, P., et al. (2012). Functional dysbiosis within the gut microbiota of patients with constipated-irritable bowel syndrome. *Aliment. Pharmacol. Ther.* 35, 828–838. doi: 10.1111/j.1365-2036.2012.05007.x

[3] Durbán, A., Abellán, J. J., Jiménez-Hernández, N., Salgado, P., Ponce, M., Ponce, J., et al. (2012). Structural alterations of faecal and mucosa-associated bacterial communities in irritable bowel syndrome. *Environ. Microbiol. Rep.* 4, 242–247. doi: 10.1111/j.1758-2229.2012.00327.x

[4] Jeffery, I. B., das, A., O'Herlihy, E., Coughlan, S., Cisek, K., Moore, M., et al. (2020). Differences in fecal microbiomes and metabolomes of people with vs without irritable bowel syndrome and bile acid malabsorption. *Gastroenterology* 158, 1016–28.e8. doi: 10.1053/j.gastro.2019.11.301

[5] Wang, T., Cai, G., Qiu, Y., Fei, N., Zhang, M., Pang, X., et al. (2012). Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers. *ISME J.* 6, 320–329. doi: 10.1038/ismej.2011.109

[6] Scheperjans, F., Aho, V., Pereira, P. A., Koskinen, K., Paulin, L., Pekkonen, E., et al. (2015). Gut microbiota are related to Parkinson's disease and clinical phenotype. *Mov. Disord.* 30, 350–358. doi: 10.1002/mds.26069

[7] Son, J. S., Zheng, L. J., Rowehl, L. M., Tian, X., Zhang, Y., Zhu, W., et al. (2015). Comparison of fecal microbiota in children with autism Spectrum disorders and Neurotypical siblings in the Simons simplex collection. *PLoS One* 10:e0137725. doi: 10.1371/journal.pone.0137725

[8] Zhu, L., Baker, S. S., Gill, C., Liu, W., Alkhouri, R., Baker, R. D., et al. (2013). Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. *Hepatology* 57, 601–609. doi: 10.1002/hep.26093

[9] Ramanan D, Tang MS, Bowcutt R, Loke P, Cadwell K. Bacterial sensor Nod2 prevents inflammation of the small intestine by restricting the expansion of the commensal Bacteroides vulgatus. Immunity. 2014;41(2):311–24.

[10] Kim YG, Kamada N, Shaw MH, Warner N, Chen GY, Franchi L, Núñez G. The Nod2 sensor promotes intestinal pathogen eradication via the chemokine CCL2-dependent recruitment of inflammatory monocytes. Immunity. 2011;34(5):769–80.

[11] Levy M, Thaiss CA, Zeevi D, Dohnalová L, Zilberman-Schapira G, Mahdi JA, David E, Savidor A, Korem T, Herzig Y, et al. Microbiota-modulated metabolites shape the intestinal microenvironment by regulating NLRP6 inflammasome signaling. Cell. 2015;163(6):1428–43.

[12] Sierra S, Lara-Villoslada F, Sempere L, Olivares M, Boza J, Xaus J. Intestinal and immunological effects of daily oral administration of Lactobacillus salivarius CECT5713 to healthy adults. Anaerobe. 2010;16(3):195–200.

[13] Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, Molina DA, Salcedo R, Back T, Cramer S, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science. 2013;342(6161):967–70.

[14] Egger, G. & Dixon, J. Beyond obesity and lifestyle: a review of 21st century chronic disease determinants. Biomed Res. Int. 2014, 731685 (2014).

[15] Maekawa, T. et al. Porphyromonas gingivalis manipulates complement and TLR signaling to uncouple bacterial clearance from inflammation and promote dysbiosis. Cell Host Microbe 15, 768–778 (2014).

[16] Sandler, R. H. et al. Short-term benefit from oral vancomycin treatment of regressive-onset autism. J. Child Neurol. 15, 429–435 (2000).

[17] Chang, P. V., Hao, L., Offermanns, S. & Medzhitov, R. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. Proc. Natl Acad. Sci. USA 111, 2247–2252 (2014).

[18] Chen, J. et al. Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. Sci. Rep. 6, 28484 (2016).

[19] Scher, J. U. et al. Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis. eLife 2, e01202 (2013).

[20] Gomez de Aguero, M. et al. The maternal microbiota drives early postnatal innate immune development. Science 351, 1296–1302 (2016).