

8th edition - 2019

Diet, Nutrition and the Gut Microbiome

Miami, FL (USA)

Current understanding of the human gut microbiome: where are we?

Our understanding of the close relationship between the human body and its associated microorganisms is rapidly expanding. Recent technological advances have enabled scientists to better understand and observe large microbial communities across time in and on the human body.

Of all the sites in and on the body, the digestive tract houses the most dense and diverse collection of microorganisms. Those microorganisms can interact with body systems, including the nervous, immune, and endocrine systems.

The gut microbiome* is a chemical factory involved in producing metabolites that affect health, including short-chain fatty acids (SCFAs)* and tryptophan metabolites. At the same time, gut microbial communities can also alter metabolites that are produced by the host, such as bile acids, and can even



modulate the efficacy and toxicity of drugs. As a result, the gastrointestinal tract is no longer seen as just a tube where nutrients are digested and absorbed.

The human microbiome has been shown to be highly dynamic and **diet is considered one of the environmental factors with the most significant influence in shaping**

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gut microbial metabolism. As **gut microbiome responses to nutrition are personalized**, one shared idea across the Gut Microbiota for Health World Summit 2019 is that we are moving from a “one-size-fits-all” dietary approach to an integrated personalized microbiome treatment approach.

Looking after our gut microbiota* is like lawn care. In order to maintain our gut microbial lawn healthy, adding compounds that promote the growth of beneficial microbes is crucial. Carbohydrates found in plants are the most well-studied diet component in relation to the modification of the human gut microbiota. Indeed, scientists have proposed the term microbiota-accessible carbohydrates* to refer to the types of dietary fiber that can be metabolically used by gut microbes.

Based on the effects of long-term diet on gut microbiome composition, modulating diet is an opportu-

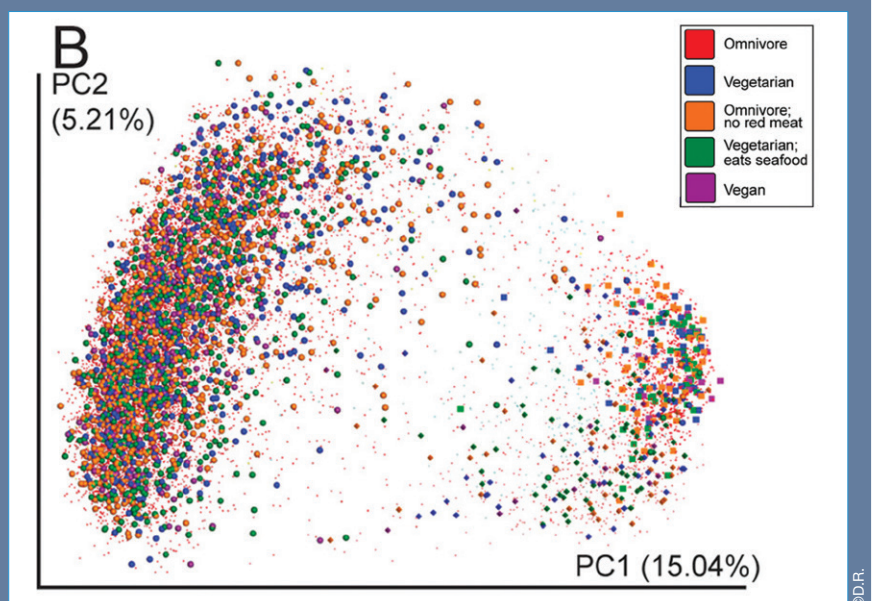
nity to change the gut microbiome with implications for a wide range of conditions including infection-related complications following elective surgery, cardiometabolic disease and even mental health.

Diet changes, infections, antibiotics and other drugs may lead to dysbiosis* of the gut microbiome. Dysbiosis can be defined as an altered stable microbiome that causes harm to the host. **Jack Gilbert from the University of California in San Diego acknowledged that dysbiosis is more than just an imbalance in gut microbial diversity** and, thus, diversity alone is not a reliable indicator to assess the health of the microbiota. Instead, **rather than establishing microbiota composition causality in disease, we should move towards exploring the dynamic functions of the gut microbiota that vary within each host and across health and disease.** ■

Diet is considered one of the environmental factors with the most significant influence in shaping gut microbial metabolism.

We are moving from a “one-size-fits-all” dietary approach to an integrated personalized microbiome treatment approach.

Data from the American Gut Project has revealed that the diversity of plants that a subject consumes is associated with microbial diversity. Consuming more than 30 types of plants per week and consuming more vegetables and fruits was associated with a higher abundance of conjugated linoleic acid – which is generally related to reduced inflammation and cardiovascular disease – and a reduction in certain antibiotic resistance genes. The fact that microbial communities tend to group by macronutrient and micronutrient intake levels in a person diet rather than by diet type highlights the contribution of dietary nutrients in regulating gut microbial metabolism.



The gut microbiota communities failed to group together by diet type. Source: McDonald D et al, *mSystems* 2018 ; 3(3) : e00031-18.

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Diet and lifestyle modulation of the gut microbiota

How can we fine-tune the gut microbiome to improve human wellness and fight against disease?

1. Diet macronutrients

PROTEINS

Recently scientists have started to focus on the role of other nutrients behind microbiota-accessible carbohydrates found in dietary fiber in shaping the gut ecosystem. Suzanne Devkota from Cedars-Sinai Medical Center and the University of California in Los Angeles focused on the importance of an adequate balance of macronutrients in a person diet, especially proteins, for preserving gut microbial diversity.

There is growing recognition that **composition and metabolic activity of the gut microbiota can be modulated by type and amount of the dietary proteins**, which in turn impact health. Reciprocally, it appears that the gut microbiota can affect protein metabolism.

Although SCFAs are derived mainly from fiber fermentation, they can also be synthesized from bacterial

metabolism of amino acids. Other metabolites of amino acid metabolism include branched chain fatty acids, indoles and amines, all of which can affect human health. For example, imidazole propionate is a microbially produced histidine-derived metabolite present at higher concentrations in subjects with type 2 diabetes.

The source of dietary protein also determines the contribution of gut microbiota on protein effects on health. Animal-based proteins may influence insulin sensitivity and diabetes through increasing counts of certain gut bacterial groups and the gut microbiota-derived metabolite trimethylamine N-oxide (TMAO), which has been involved in the development of atherosclerosis.

However, Karine Clément from Pitié-Salpêtrière Hospital in Paris said that it is important to acknowledge that **the impact of animal protein intake on insulin resistance does not**

Plant-based proteins have a less negative impact on cardiovascular disease risk through a shift in the bacterial metabolites with increased levels of the SCFAs, i.e., acetate, propionate, and butyrate.



“The gut microbiota role in dietary protein metabolism and health-related outcomes is different depending on each person gut microbiota’s profile (enterotype and richness).”

Karine Clément



Proteins can serve as nitrogen and energy sources for gut bacteria and chronic low protein diets induce a lack of essential amino acids that is perceived by the body as a nutritional stress. In this context, **a supplementation with mixed fiber types (cellulose and inulin) allows the gut microbiota amino acid biosynthesis through the utilization of cellulose as an alternative carbon source.**

work the same for everybody as it depends on each person gut microbiota's profile (enterotype* and gut microbial gene richness). By contrast, plant-based proteins have a less negative impact on cardiovascular disease risk through a shift in the bacterial metabolites with increased levels of the SCFAs, i.e., acetate, propionate, and butyrate.

DIETARY FIBERS

The gut microbiota has developed metabolic capacities that we as humans are unable to perform.

Strikingly, the benefits of dietary fibers on host metabolism can be explained by the existence of different bacteria species within the gut ecosystem that evolved in the same way and exploited the same dietary substrate as a group (named gut microbiota 'guilds'). As different gut bacteria have different nutritional requirements, **these results support the benefits of increasing both the amount and the variety of dietary**

fibers ingested for improving metabolic diseases.

DIETARY SUGARS

Some dietary sugars can alter the structure and function of the gut microbiota and may be responsible for the severity of *Clostridium difficile* infections.

Thus, it appears that certain hyper-virulent strains of *C. difficile* have independently acquired mechanisms to metabolize even low concentrations of trehalose. Robert Britton and colleagues have also shown that this ability to metabolize trehalose is associated with disease severity in mice. Whether these findings replicate in humans needs to be confirmed.

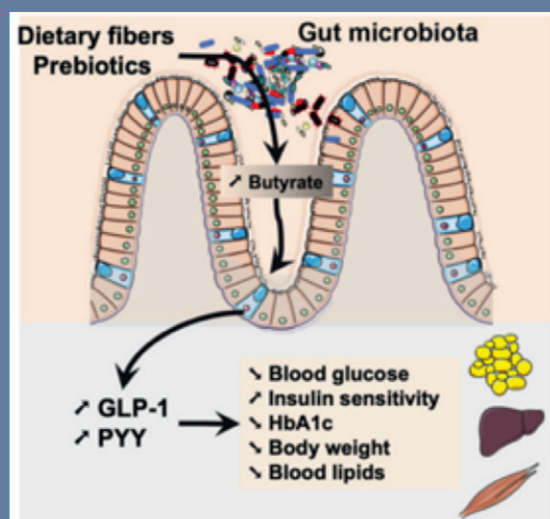
2. Diet micronutrients

Most research has focused on the effects of macronutrients (especially carbohydrates and proteins and more recently fats) on the gut mi-

Robert Britton from the Baylor College of Medicine in Houston (Texas, USA) explained that, based on animal data, **the growing use of the sugar trehalose** – it occurs naturally in mushrooms, honey, lobsters and bakery foods and it can also be used as food additive in frozen foods, jams, instant noodles and fruit juices – **may contribute to explain the virulence and global spread of epidemic healthcare-associated *C. difficile***. These novel findings contribute to explain the current rise of non-antibiotic-associated *C. difficile* infection cases.

Liping Zhao reported the results of a small clinical trial of dietary manipulation of the gut microbiota in patients with diabetes treated with acarbose, which is an anti-diabetic drug that reduces the digestibility of dietary starches so that they reach the colon where they are fermented by the gut microbiota. **Increasing the quantity of nondigestible carbohydrates¹ that reach the gut improved the metabolic parameters of patients with type 2 diabetes.** The causal involvement of these findings was confirmed when mice were colonized with the gut microbiota from participants post-intervention.

¹ - Composition of the experimental diet: The experimental diet consists of a mixture of several components rich in dietary fibers and traditional Chinese medicinal food plants, including extracts from wholegrains including buckwheat, Job's tears (*Coix lachrymal-jobi L*), oat, white bean, yellow corn, red bean, yam, peanut, lotus seed, bitter melon, kudzu starch, Inulin, and resistant dextrin. The diet contains diverse type of fibers including β -glucans, arabinoxylans, cellulose, hemicellulose, resistant starches, gums, and oligosaccharides.



Targeted modulation of the gut microbiota with dietary fibers and prebiotics* improves metabolism.
Source: *Cani PD, Kidney Int 2019 ; 95(1): 14-6.*



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crobiota. Although colonic microorganisms also play a part in vitamin synthesis and in absorption of calcium, magnesium and iron, **little is known about the effects of micronutrients on the human microbiota.**

Joseph Zackular from the University of Pennsylvania strengthened that despite micronutrients are essential in host immunity against pathogens, when their levels are excessive may have detrimental effects in the gut ecosystem.

The fine-tune crosstalk between micronutrients and the gut microbiota was illustrated by the case of zinc. In situations of deficiency, zinc supplementation has been used for immune modulation in the context of inflammatory diseases and in protein energy malnutrition. However, under conditions of health and normal metal intake, excess dietary zinc can alter the gut microbiota and increase the risk and severity of *C. difficile* infection.

3. Probiotics

The American Gastroenterological Association is working on a new clinical guideline of probiotics* in the prevention and treatment of adult and pediatric gastrointestinal conditions.

Purna Kashyap from Mayo Clinic and Geoffrey Preidis from the Baylor College of Medicine presented data from different levels of evidence that supports the use of probiotics in the management of gastrointestinal disease:

- Management of and prevention of *Clostridium difficile*.
- Management of inflammatory bowel disease* (Crohn's disease, ulcerative colitis and pouchitis).
- Management of irritable bowel syndrome (IBS)*.
- Management of infectious gastroenteritis.
- Management of *Helicobacter pylori*.

The three key elements outlined to help physicians determine the validity of a probiotic include:

1. Evidence that the strain has been tested in well-designed human trials, in either a heterogeneous population or stratified based on defined characteristics of host or microbial genomics.
2. The dose and viability in the product are equal to that of the human trials.
3. Whole genomic strain characterization and transparency declared strain designation are provided.

Beyond clinical evidence supporting the effectiveness of probiotics for the prevention or treatment of specific gastrointestinal diseases, Pinaki Panigrahi from the University of Nebraska Medical Center presented findings on the largest randomized trial to date about the use of a synbiotic to prevent sepsis among infants in rural India.

Excess dietary zinc can alter the gut microbiota and increase the risk and severity of *C. difficile* infection.

A synbiotic mix showed a reduction in the risk of infections up to 82% by Gram-positive bacteria.

GutMicrobiota Health @GMFH1x

Learn more about Panigrahi's research on how a synbiotic improves the incidence rate of sepsis in children in our post from Paul Enck gutmicrobiotaforhealth.com/en/large-clini... #GMFH2019

A large clinical trial in India finds a synbiotic may help prevent neonatal sep...
Sepsis is a life-threatening condition characterized by systemic inflammation; it is one of the major contributors to neonatal mortality, especially in developing coun...

08/15 - 24 mars 2019

15 Retweets 23 J'aime

Amy Karon @amykaron

Probiotics might reduce risk of *C. difficile*-associated diarrhea by as much as 60%. #gmfh2019 @MDEdgeTweets

Probiotics for Prevention of Clostridioides difficile-Associated Diarrhea - Summary

- These studies suggest that probiotics reduce the risk of CDAD by 60%
- Effects are more pronounced in high-risk populations
- CRADIC = moxifloxacin
- Results were similar for:
 - Adults vs children
 - Inpatients vs outpatients
 - Different probiotic strains
 - Lower vs higher doses
 - Studies with high vs low risk of bias

08/24 - 24 mars 2019

4 Retweets 6 J'aime



There is current evidence of a relationship between exercise and fitness and the gut microbiome and metabolites.

The follow up of 4,556 infants 60 days after treatment with a combination of *Lactobacillus plantarum* ATCC strain 202195 with fructooligosaccharide (the synbiotic mix) showed a reduction in the risk of infections up to 82% by Gram-positive bacteria. Panigrahi is working now with the government in testing the same approach in different settings.

4. Lifestyle

Beyond the traditional health benefits of physical exercise, Paul Cotter from the University College Cork shared the current evidence of a relationship between exercise and fitness and the gut microbiome and metabolites.

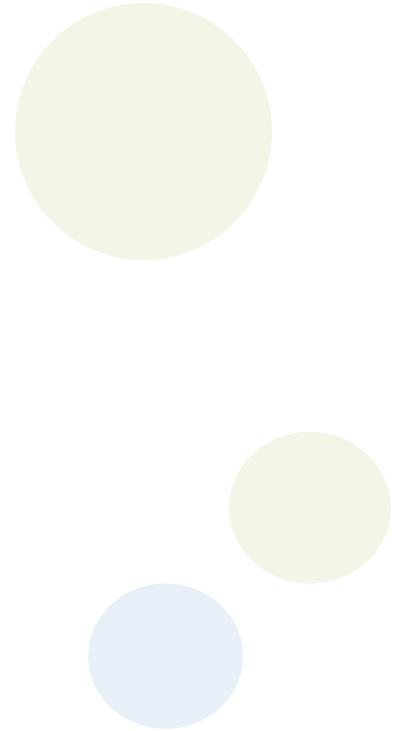
There is a complex relationship between diet, exercise and the gut microbiome. Cotter's group findings indicate that "exercise is another

important factor in the relationship between the gut microbiota, host immunity and host inflammation, with diet playing an important role".

Beyond changes in gut microbial diversity, exercise may lead to changes at the functional metabolic level, which is supported by the increased in metabolic pathways (eg, carbohydrate metabolism) and faecal metabolites (eg, microbial produced SCFAs) associated with enhanced muscle turnover and overall health.

Overall, exercise over an extended period (fitness) is required for more substantial changes on the gut microbiome.

Even in patients with quiescent inflammatory bowel disease, a 8-week program of aerobic and resistance exercise can safely achieve body compositional changes without adverse effects. ■



“In addition to helping control weight, exercise can have a beneficial influence on your health due to its impact on your gut microbes.”

Paul Cotter

Gut microbiota as a target for gut, metabolic and liver conditions

Microbiota-derived metabolites as a new therapeutic approach

The human distal intestine is a highly efficient bioreactor in terms of the huge diversity of by-products produced by gut microorganisms.

Gut microbial metabolism yields hundreds of unique chemicals ranging from short and branched chain fatty acids to vitamins and lipids, which vary across individuals. **Dylan Dodd from Stanford University focused on targeting microbiota-derived metabolites as an emerging therapeutic modality not only for gastrointestinal conditions, but also on nutrition processes, central nervous system activity, cardiovascular health and renal system.**

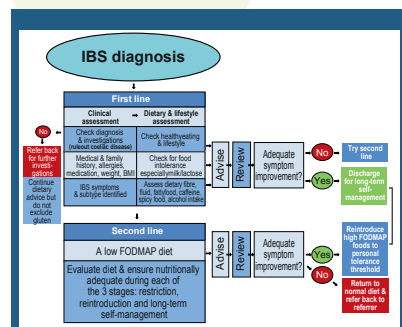
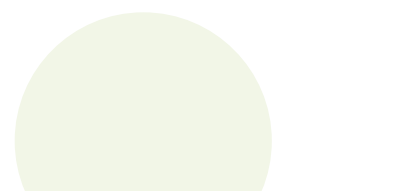
On the whole, commensal organisms of the human microbiota can produce a huge number of small molecules with an equally diverse array of targets that can impact human health and disease. As a result, **strategies for controlling metabolic**

output in the gut through mapping specific metabolites may benefit host physiology in the future.

Functional gastrointestinal disorders

The current development of new treatment alternatives for functional gastrointestinal disorders and IBS in particular involves that modulating the gut microbiota might be relevant for a substantial proportion of these patients.

The majority of patients with IBS report worsening of symptoms after intake of certain food items, particularly foods containing carbohydrates and fat. When the first line dietary and lifestyle assessment is not accompanied by an adequate symptom improvement, several published clinical trials support the use of a diet low in fermentable oligo-, di- and monosaccharides and polyols (FODMAP) for managing symptoms through its impact on the gut microbial community.

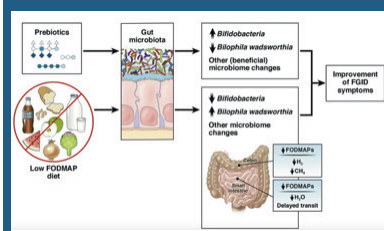


IBS dietary algorithm. Source: McKenzie YA et al, *J Hum Nutr Diet* 2016 ; 29(5): 549-75.

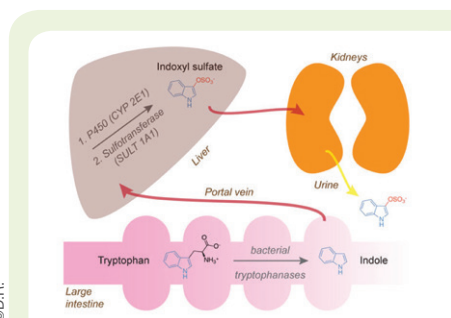
Magnus Simrén from the University of Gothenburg emphasized that **the long-term management of IBS through a low FODMAP diet may lead to detrimental effects on the gut microbiota secondary to the reduced prebiotic intake.**

Furthermore, not all IBS patients respond favorably to a low FODMAP diet and the current challenge is identifying those IBS patients who are more likely to benefit from a low FODMAP diet. In this way, the gut microbiota composition and function (i.e., fecal volatile organic compounds) might be used to predict response to dietary intervention in patients with IBS.

Beyond FODMAP diet, other approaches including a Mediterranean-type diet with a prebiotic supplement and probiotics might be an alternative to dietary restriction for patients with functional gut symptoms.



Modulating the gut microbiota as a treatment strategy for IBS. Source: Simrén M, *Gastroenterology* 2018 ; 155(4):960-2.



Teamwork between the host and microbiota in production of indoxyl sulfate. Source: Devlin AS et al, *Cell Host Microbe* 2016 ; 20(6): 709-15.

To cite an example, altering the abundance of the gut commensal *Bacteroides* tryptophanase harboring a family of genes (named tryptophanases) allows to modulate the levels of indoxyl sulfate, which is a uremic toxin found in higher concentrations in kidney disease whereas is maintained at low levels in healthy individuals. These results show that targeting the microbiota might help in controlling host indoxyl sulfate levels and suggest a possible strategy for treating renal disease.

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Metabolic conditions

The microbiome and related metabolites are involved in several features by which certain lifestyle factors may predispose to obesity and diabetes. Christoph A. Thaiss from the University of Pennsylvania updated the molecular and cellular mechanisms by which changes in human lifestyle may predispose to obesity.

According to Thaiss, the impact of the modern human lifestyle on the development of obesity and associated comorbidities may arise from:

- Disturbances in the diurnal changes in composition and function of the intestinal microbiota.
- Microbiome “memory” in post-dieting weight regain.
- Enhanced susceptibility to enteric infections associated by defective intestinal barrier facilitated by hyperglycemia.

Beyond the contributory role of intestinal microbes to metabolic diseases, emerging evidence shows the **gut microbiome as a potential target for the prevention or treatment of cardiometabolic diseases.**

High levels of TMAO has been involved in atherosclerosis and heart disease. Stanley Hazen from the Cleveland Clinic explained that, more intriguingly, the production of TMAO from dietary phosphatidylcholine is dependent on gut microbiota, which opens the possibility to attenuate atherosclerosis through novel strategies:

- Modifying the diet to limit the intake of choline-rich food (with

major sources including eggs, liver, beef, and pork).

- Altering the gut microbiota through suitable probiotic bacteria with limited capacity to produce trimethylamine from choline
- Suppressing the synthesis of TMAO pharmacology.

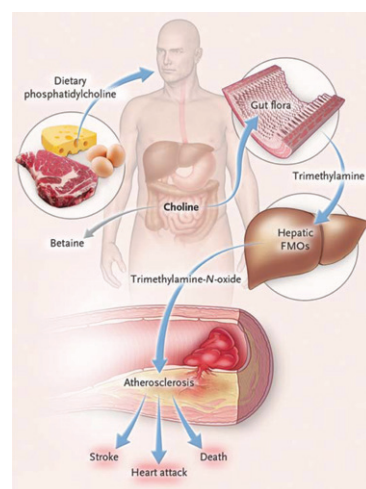
Altogether, these findings support that **interfering on gut bacteria metabolites (sometimes named “post-biotics”*) with an effect on host health is emerging as a new therapeutic approach that enable us to counteract the rapid rise of metabolic diseases.** Microbial enzymes are also emerging a potential target for drug development efforts.

Liver disease

The role of gut microbiome in liver disease is supported by the presence of bacteria in the blood, increased blood lipopolysaccharide (LPS) levels and bacteria overgrowth in the small intestine.

Rohit Loomba from the University of California at San Diego provided clinical evidence on gut microbiome alteration in patients with hepatic steatosis. Therefore, gut microbiome and its metabolites, specifically aromatic amino acids and branched-chain amino acids, emerge as potential non-invasive biomarkers that allow detection of advanced fibrosis in human nonalcoholic fatty liver disease.

Future gut microbiome therapeutic strategies are likely to target early stages of liver disease. ■



Relationship between dietary phosphatidylcholine, intestinal microbiota and atherosclerosis.

Source: Tang WH et al, *N Engl J Med* 2013; 368(17): 1575-84.



23 POSTERS

A total of 23 new posters about gut microbiota-related experimental and clinical studies from researchers from all over the world were presented during a networking session at #GMFH2019



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Suivre

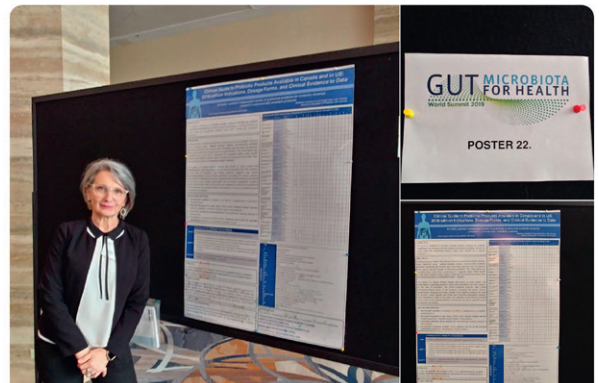
23 novel #gutmicrobiome abstracts were presented at #GMFH2019. You can review them here: ow.ly/GVsc30oasUO



Dragana Skokovic-Sunjic
@ProbioticDr

Suivre

Ready for poster session #GMFH2019
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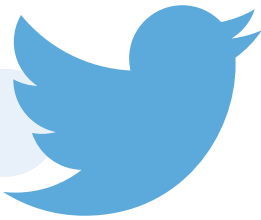
Conclusion

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Environmental factors related to diet are larger determinants of gut microbiota composition. Gut microbiome and metabolome*-targeted interventions through diet and lifestyle are paving the way towards more effective diagnosis, treatment and preventive modalities to improve not only gastrointestinal health but also other prevalent conditions such as metabolic and liver diseases.

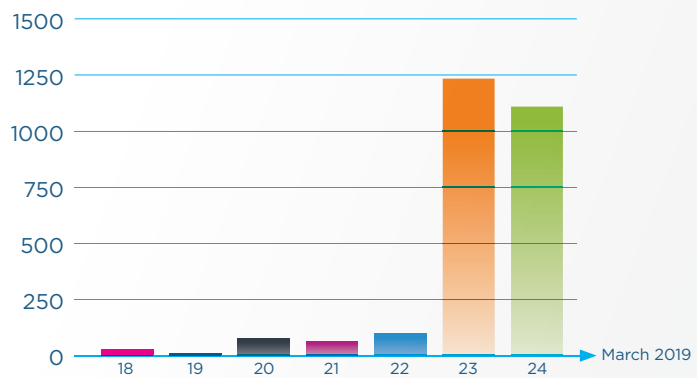
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#GMFH2019
the summit
went viral



Gut Summit 2019 was trending topic in Miami during the 2 days event and it was accompanied with interactive conversations on Twitter. We thank the 69 influencers from US, Canada, France, Mexico, Ireland, Brussels, among others, who have been active in the #GMFH2019 conversation.

Tweet Activity of #GMFH2019



10.990M

Impressions

2,378

Tweets

471

Participants

752

Avg Tweets/Hour

5

Avg Tweets/Participant



GLOSSARY

Dysbiosis: perturbed microbial ecosystem compared with the healthy state or homeostasis. Instead of being measured by species richness or diversity, scientists highlight that functional diversity, stability and resilience also matter when assessing the health of the microbiota and the host.

Enterotype: groups of gut bacteria classified according to the most abundant genus. Communities of gut bacteria may form a spectrum rather than falling into distinct groups.

Fermented foods: foods or beverages made by extensive microbial growth. Those fermented foods containing live organisms that have been characterized and have clinical evidence of a health benefit are considered probiotics. For example, many fermented milks have probiotic activity for conditions related to the digestive tract and the immune system.

Inflammatory bowel disease (IBD): is an umbrella term used to describe disorders characterized by an excessive swelling of the wall of one section of the digestive tract. Types of IBD include Crohn's disease, ulcerative colitis and pouchitis that are. Both genetic and environmental factors potentially affect microbiota composition, which plays a role in IBD pathogenesis.

Irritable bowel syndrome (IBS): common functional disorder affecting up to 20% of people worldwide, with a higher prevalence in women. It is indeed the main motivation behind gastroenterology conditions. Researchers believe it may originate from an unbalanced gut microbiota.

Metabolome: the complete set of small-molecule chemicals found in a cell, tissue or organism. The gut microbiota is an important producer of short-chain fatty acids, which are produced by bacterial fermentation of dietary fibers and have health benefits both in the gut and distant body sites.

Metagenome: the entire genetic material present in a sample, including both the genomes of human cells and of the gut microorganisms.

Microbiome: is used for two concepts. One to refer to the collective genomes harbored by microbes, and another one to refer to the entire habitat, including the microorganisms and their genomes. Nowadays, this term is commonly used to refer to the microorganisms themselves.

Microbiota: the community of micro-organisms living in a specific environment. For example, 'the gut microbiota' refers to all microbial communities within the intestinal tract.

Microbiota-accessible carbohydrates (MACs): dietary carbohydrates that are resistant to degradation and absorption by the host and are extensively metabolized by the intestinal microbiota.

Microbiota diversity: a measure of the number of species and how individual bacteria are distributed in the community. Lower diversity is considered a marker of gut dysbiosis.

Postbiotics: bacterial metabolites with a direct effect on host nutrition, metabolism and immunity (eg, short-chain fatty acids).

Prebiotics: these are substrates that are selectively utilized by host microorganisms conferring health benefits. Not all food fibers are considered prebiotics as selective utilization by gut bacteria is a requirement for a prebiotic.

Probiotics: these are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host.

Short-chain fatty acids: fatty acids with two to six carbon atoms that are produced by bacterial fermentation of dietary fibers (e.g., acetate, propionate, and butyrate).

GUT MICROBIOTA FOR HEALTH

World Summit 2020



**SATURDAY 7 AND
SUNDAY 8 MARCH, 2020**

MADRID (SPAIN)
RUI PLAZA ESPAÑA HOTEL

**SAVE
THE
DATE**

9th edition

of the primary event
on gut microbiota and health,
addressed to clinical
researchers and healthcare practitioners

2 days of plenary sessions
and workshops



with the
support of



The Gut Microbiota For Health World Summit is a scientific event sponsored by the European Society for Neurogastroenterology & Motility, the American Gastroenterological Association and the European Society for Paediatric Gastroenterology Hepatology and Nutrition.