Food and Agriculture Organization of the United Nations

The role of microbiome science in addressing malnutrition and noncommunicable diseases

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Food and Agriculture Organization of the United Nations
Rome, 2024

Fontaine, F., Bessy, C., Delzenne, N.M., Diaz-Amigo, C., Koren, O., Laorden, C., Lartey, A., O'Keefe, S., Sonnenburg, J. and Callens, K. 2024. *The role of microbiome science in addressing malnutrition and noncommunicable diseases.* Rome, FAO.
https://doi.org/10.4060/cd1778en

ISBN 978-92-5-139001-6

Cover: Art&Design Srl

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Abbreviations

ADI	acceptable daily intake
BMI	body mass index
CVD	cardiovascular disease
FAO	Food and Agriculture Organization of the United Nations
FBDGs	food-based dietary guidelines
FMT	faecal microbiome transplant
FOS	fructooligosaccharides
GOS	galactooligosaccharides
HFD	high-fat diet
HICs	high-income countries
HMO	human milk oligosaccharide
IBD	inflammatory bowel disease
IHMC	International Human Microbiome Consortium
ISAPP	International Scientific Association for Probiotics and Prebiotics
LMICs	low- and middle-income countries
MAC	microbiota-accessible carbohydrate
MAM	moderate acute malnutrition
MDF	microbiota-directed food
ML	maximum level
MRL	maximum residue level or maximum residue limit
NAFLD	non-alcoholic fatty liver disease
NCD	non-communicable disease
NOEL	no observed effect level
RCT	randomized controlled trial
RUSF	ready-to-use supplementary food
SAM	severe acute malnutrition
SCFA	short-chain fatty acid
SDG	Sustainable Development Goal
STORMS	Strengthening The Organization and Reporting of Microbiome Studies
TMAO	trimethylamine N-oxide
WHO	World Health Organization

Glossary of terms

Biotics: In this paper, the term refers to a group of products (e.g. prebiotics, probiotics, synbiotics and postbiotics) that can be used to modulate the gut microbiome and confer health benefits on the host.

Diversity: Usually refers to "alpha-diversity" – a measure of how many different species (richness) are present in the microbiota. Lower diversity is among several criteria that are considered markers of an unhealthy microbiome.

Dysbiosis: The compositional and functional alterations in the microbiota of individuals with disease, as compared with healthy individuals. This term does not address the causality of the microbiome in pathologies.

Faecal microbiome transplant (FMT): A transfer of intestinal or stool microbiota from a donor, into the digestive tract of a recipient. The procedure may be used experimentally to address the causality of the microbiome in a given pathology. It is also a potential therapeutic approach, for example for the treatment of recurrent Clostridium difficile infection.

Germ-free animals: Animals that have no microorganisms living in or on them. Controlled microbiome transplantation (including from humans) to germ-free animals can be used to study the interactions between host and microbiome, and the impact of specific environmental factors. They are essential assets for studying causality.

Microbial metabolites: Substances resulting from the microbial metabolism that potentially affect the host physiology. They can be produced from exogenous dietary (or non-dietary) substrates, or endogenous host compounds. Such metabolites are key factors in host–microbiome crosstalk. Examples of microbial metabolites include short-chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO).

Microbiome: All microorganisms of a given environment (microbiota) and their "theatre of activity" – meaning all their genetic material, microbial structures, and metabolites (Berg *et al.*, 2020).

Microbiota: The microbial community (comprising bacteria, archaea, fungi, unicellular eukaryotes and viruses) that is specific to a particular habitat.

Omics: Refers to a set of techniques that allow for the analysis of diverse pools of biological molecules. Examples include genomics for DNA, transcriptomics for RNA, proteomics for protein and metabolomics for metabolites. When applied to microbial populations, they can potentially provide data on the taxonomy and abundance of microorganisms and their functions, through information on the functional genes (e.g. metagenomics), active metabolic pathways (transcriptomics and proteomics), and metabolite production (metabolomics) in a given sample at a given time.

Personalized nutrition: A field that leverages human individuality to drive nutrition strategies that prevent, manage and treat disease, and optimize health. An individual's microbiome data can be used in addition to genetic, phenotypic, medical, nutritional and other relevant information to deliver more specific healthy eating guidance, along with other nutritional products and services (Bush *et al.*, 2020).

Postbiotic: A "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" (Salminen *et al.*, 2021, p. 1).

Prebiotic: Refers to a "substrate that is selectively utilized by host microorganisms conferring a health benefit" (Gibson *et al.*, 2017, p. 3).

Probiotic: Refers to "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (Hill *et al.*, 2014, p. 507).

Synbiotic: Refers to "a mixture, comprising live microorganisms and substrate(s) selectively utilized by host microorganisms, that confers a health benefit on the host" (Swanson *et al.* 2019, p. 1).

Acknowledgements

The research and drafting of this paper were carried out by Fanette Fontaine of the Food and Agriculture Organization of the United Nations (FAO), under the technical leadership and guidance of Karel Callens (FAO). Carmen Diaz-Amigo (FAO) and Catherine Bessy (FAO) contributed to sections 3.3 and 5.

For their insightful contributions to various sections, FAO is grateful to the following experts: Nathalie M. Delzenne (University of Louvain, Belgium), Omry Koren (Bar-Ilan University, Israel), Carlos Laorden (World Trade Organization, Switzerland), Anna Lartey (University of Ghana, Ghana), Stephen O'Keefe (Stellenbosch University, South Africa) and Justin Sonnenburg (Stanford University, United States of America).

The authors would like to thank Dalia Mattioni (University of Pisa, Italy), Lynnette Neufeld (FAO), Maria Xipsiti (FAO) and Liping Zhao (Rutgers University, United States of America) for their review of the paper. Our appreciation also goes to Andi Shiraz for editing, Davide Moretti for graphic design and layout, and Chiara Deligia (FAO) for coordinating the publishing process.

Executive summary

Despite modest progress, stunting and wasting in infants and young children in some contexts, and micronutrient deficiency in women and children in most contexts, continue to be major concerns for global public health. In addition, the world is witnessing a global and unprecedented rise in the prevalence of obesity and diet-related noncommunicable diseases (NCDs). No country has made substantial progress in halting or reversing this trend. All forms of malnutrition are multicausal and much has been elucidated on these pathways, including the centrality of unhealthy diets as a common cause of all forms of malnutrition. Despite this evidence, an incomplete understanding of biological pathways to malnutrition may limit the capacity to design and implement effective prevention and treatment measures. A growing body of evidence shows that humans have a symbiotic relationship with the community of billions of microorganisms present in their intestines – the gut microbiome – and that this may have crucial implications for nutrition and health.

This paper provides a narrative review of the state of knowledge on the human gut microbiome – including its origins, development and relation to nutrition and health. Based on this review, it explores the potential implications of current evidence for actions to prevent and treat various forms of malnutrition, and discusses further directions for research.

The gut microbiome is deeply involved in host physiology via, among others, the production of metabolites that are involved in the regulation of various host functions. These include digestion, metabolism, gut–brain communication, and the immune system. Disturbances in gut microbiome functions and composition (such as loss of biodiversity, loss of beneficial bacteria, and increase of pathogens) are often referred to as dysbiosis, and are associated with several forms of malnutrition, as well as some diet-related NCDs. A range of environmental factors can either disturb or enhance the symbiotic relationship between humans and their microbiomes, with major implications for human health. These factors apply not only during a child's developmental period, but throughout life.

The gut microbiome is first acquired during birth, by vertical transmission from the mother. But evidence suggests that dietary patterns throughout life may foster or hinder the development and maintenance of the gut microbiome. For example, maternal diet and early life feeding practices are key factors that impact the development of a healthy gut microbiome during the first three years of life. For the years of life that follow, health-supporting microbiomes have been linked to diets that are high in dietary fibre and phytonutrients – resulting from the consumption of a high diversity of plant foods, minimally processed (rather than highly processed) foods, and fermented foods. There is some evidence that the microbiome mediates some of the known effects of diet on health, and microbiome studies have also provided new insights on the interconnectivity of nutrition and health.

Based on the scientific knowledge available, the paper reviews a range of microbiome-based innovations and dietary interventions that could help to address not only NCDs, but all forms of malnutrition – including for example through targeted "biotics" approaches (i.e. pre-, pro-, post- and synbiotics) and microbiota-directed foods (MDFs). Some of these products have shown positive results in randomized controlled trials (such as MDFs for undernutrition), but more evidence is needed to inform and ensure compliance with appropriate regulatory frameworks and health claims. One of the innovations derived from microbiome science involves the possibility of modulating an individual's diet based on their specific microbiome, with the aim of tackling their specific health issues (i.e. personalized nutrition).

Microbiome data also add to the established evidence that lifelong adherence to a healthy diet is critical for the prevention of all forms of malnutrition, including undernutrition, overweight, obesity and related NCDs. Healthy diets ensure essential nutrients and micronutrient adequacy without an excess of energy; they also minimize unhealthy foods and dietary components, and provide rich sources of bioactive components. In addition to those core principles, microbiome data suggest the importance of a high intake of dietary fibres, (even beyond current recommended levels); the consumption of a high diversity of un- and minimally processed plant foods; and the consumption of a range of fermented foods. All of these will favour a healthy microbiome, which in turn may further contribute to addressing several forms of malnutrition, particularly obesity and related NCDs.

Lifelong adherence to a healthy diet depends not only on the individual, but also on various other factors in agrifood systems. The paper therefore analyses possible entry points for changing consumption patterns through the agrifood system, in order to better support the gut microbiome and improve health. These entry points include nutrition and health education and consumer awareness programmes, food-based dietary guidelines (FBDGs), management and regulation of the food environment, food product development, processing and re-engineering, food production, crop diversification and breeding, and food safety risk assessment.

Realizing the full potential of microbiome science and innovation in the fight against malnutrition and NCDs is possible, but requires further research. The paper therefore discusses a range of major research gaps in this regard, along with recommendations to address them, including through the standardization of methods and protocols, interdisciplinary approaches, and citizen science. A stronger focus should also be placed on low- and middle-income countries (LMICs), to account for their specific contexts and for developments in their agrifood systems, dietary patterns, and nutrition and health outcomes.

In conclusion, microbiome science and innovation offer significant potential to inform new and practical agrifood systems actions, that can in turn help to improve strategies against against all forms of malnutrition and NCDs.

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1 Introduction

Despite significant progress in certain areas, the world is off track for meeting global nutrition targets. Hunger and malnutrition in all its forms persist. In many places, recovery from the COVID-19 pandemic has been slow, and ongoing conflicts further threaten the achievement of key nutrition goals. In some regions, undernutrition rates are in fact increasing. At the same time, we are witnessing a rapid rise in overweight and obesity worldwide. Even in low- and middle-income countries (LMICs), obesity and other diet-related non-communicable diseases (NCDs) have become an important nutrition and health concern over the past 30 years, and no country has yet been able to reverse the trend.

It has long been known that exposure to an unhealthy (i.e. inadequate, unsafe and unbalanced) diet is a direct risk factor for all forms of malnutrition and health-related outcomes (Branca *et al.*, 2019). In 2017, one out of five deaths worldwide – in both poor and rich countries – was linked to unhealthy diets (Afshin *et al.*, 2019). **In addition, many environmental factors that are strongly linked to industrialization and rapid urbanization are recognized as primary underlying causes for various forms of malnutrition and NCDs** (WHO, 2014).


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Studies also suggest that the "dietary energy imbalance" concept (i.e. an excess of dietary energy consumed, as compared to actual energy expenditure) is far from sufficient to explain, manage and reverse the obesity epidemic and address undernutrition (Camacho and Ruppel, 2017; Laster and Frame, 2019; Ludwig and Ebbeling, 2018).

A growing body of evidence shows that humans have a symbiotic relationship with the community of billions of microorganisms present in their intestines – the gut microbiome – and that this may have important implications for nutrition and health. Studies on the gut microbiome may provide additional understanding of the underlying biological pathways between diet, nutritional status, and health outcomes, which can in turn inform the design of potential solutions to the worrisome trends in undernutrition, obesity and various diet-related NCDs. For example, several studies have associated industrialization, urbanization and the subsequent nutrition transition among populations with disturbances in the gut microbiome (commonly known as dysbiosis), and the increase in NCDs. (Blaser, 2017; Frew, 2019; Sonnenburg and Sonnenburg, 2019). The gut microbiome exists at the interface between the food ingested, the gut epithelium and the host's physiology; it can therefore play a significant role in mediating some of the effects of the environment on human health.

While microbiome science is still relatively new, it has advanced rapidly, reaching the stage where some of the basic science may be relevant to inform tangible interventions for improving health and nutrition – both in high-income countries (HICs) and in LMICs. Moreover, research on the human microbiome has the potential to contribute to significant advancements in both medicine and nutrition, with important implications for agrifood systems.

This narrative review presents the state of knowledge regarding interconnections between the gut microbiome and human health, focusing in particular on obesity, undernutrition and diet-related NCDs. The paper also explores how changes in lifestyle and diet – especially early in life – can disturb or positively enhance the gut microbiome, and have potentially major impacts on human health (see **Figure 1**). It presents and discusses emerging innovations based on microbiome knowledge, and the potential implications of current evidence for actions to prevent various forms of malnutrition and related health outcomes. Major research gaps and needs, recommendations and policy implications are also addressed.

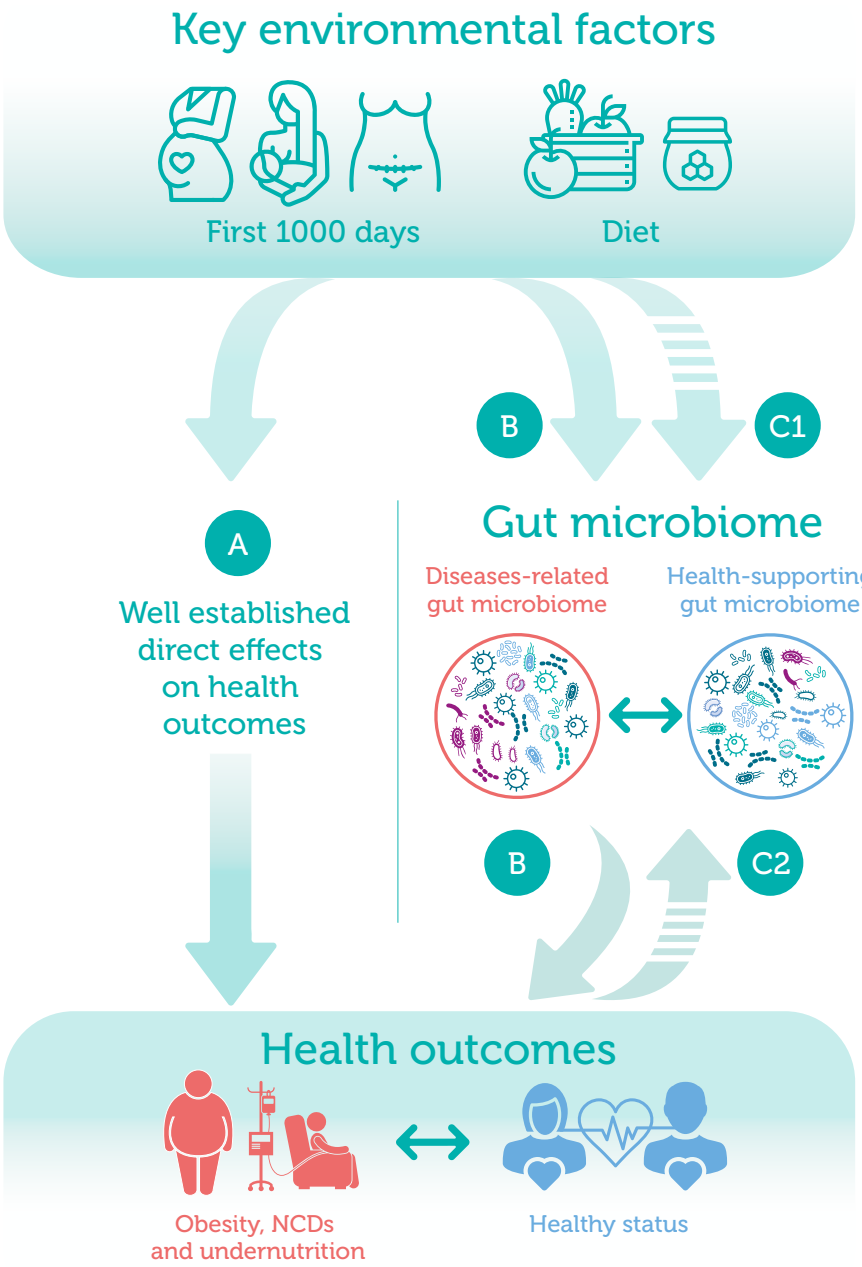

Figure 1. Interconnections between the gut microbiome, environmental factors and human health

Notes: The first 1000 days of life, along with diet, are considered key environmental factors whose direct effects on an individual's nutrition and health outcomes and overall health status are well established (as indicated in the figure by the arrow labelled A, at left). In addition however, numerous studies suggest that the gut microbiome also plays a significant role in the relationship between these environmental factors and health status. Section 2 of this paper explores the connections between the gut microbiome and health status (as indicated by the arrows labelled B and C2, at bottom), including possible causal links (arrow B, at bottom). Section 3 explores the effects of environmental factors on the microbiome (arrows B and C1, at top), along with their potential mediating role on health (arrows B, at top and bottom).

Source: Authors' own elaboration.

2

Understanding the gut microbiome and its links to nutrition and health

Although **the presence of a commensal microbial community in the human gut has been recognized for a long time (commensal as in "eating at the same table", and referring to microbes that live in or on the body without harming human health)**, microbes have, since the 19th century, mostly been associated with infectious diseases (Berg *et al.*, 2020). Because pathogenic microbes are seen as damaging to human health, extensive measures have been taken to eliminate them from our bodies, our environment and our food chains. Advances in sanitation and in the application of antimicrobials have resulted in an indisputable reduction in morbidity and mortality from infectious diseases, but these advances may have had unexpected consequences for the long-term equilibrium that has developed over time between humans and their microbial communities (Blaser, 2017; Rook, Lowry and Raison, 2013). A better understanding of both the negative and positive impacts of microbial populations living in the human gut is now possible, **based on recent technical progress in DNA sequencing and "omics" technologies, which have revolutionized our capacity to investigate the complex microbial communities that are referred to as microbiomes.**

2.1 Definition and role

A microbiome is defined as a dynamic microbial community "occupying a reasonable well-defined habitat with distinct physio-chemical properties" (Berg *et al.*, 2020, p. 17). The definition encompasses not only the sum and the interactions between microorganisms – composed of bacteria, fungi, viruses, protozoa, algae and archaea – but also its function or "theatre of activity", which includes elements such as microbial structures, metabolites and mobile genetic elements (Berg *et al.*, 2020).

Human beings host a range of microbiomes, corresponding to different body parts (e.g. skin, vagina, nose and gut). For the digestive tract alone (due to the different anatomical and environmental conditions that are found from mouth to rectum – including in terms of pH, oxygen and nutrients), several microbiomes have been identified; these include the oral, stomach, small intestine and colon microbiomes. Each of these harbours major differences in terms of number, taxonomy, dynamic and function. Because it has one of the most abundant and dense microbial populations, and because it is relatively easy to study in non-invasive ways (using faecal samples as proxy), the gut microbiome – i.e. the colon and caecum microbiome – has been the most studied, with most of this research focusing largely on the bacterial population found in the human gut. There are at least 150 times more bacterial genes than there are genes found in the human genome, and there are at least as many bacterial cells as there are human cells – with the vast majority of them in the gut (Walker and Hoyles, 2023). Indeed, each individual carries over 1000 different species of bacteria in their gut (Qin *et al.*, 2010), and gut bacteria produce hundreds to thousands of metabolites and bioactive compounds (Wishart *et al.*, 2023).

The composition of the gut microbiome is unique to each individual, but because of functional redundancy (when the same functions can be performed by different bacterial species), microbiome functions are more consistent among people with similar diets and lifestyles (Tian *et al.*, 2020). Research to reduce the complexity of the gut microbiome has therefore focused on using stratifications (i.e. enterosignatures) to try to categorize broad compositional differences between guts (Costea *et al.*, 2018; Frioux *et al.*, 2023; Tap *et al.*, 2023). The aim is to better characterize microbiome variations and to stratify individuals based on their gut microbiome composition/functions, both for diagnostics purposes and for the optimization of dietary interventions and treatments for specific groups of individuals.

Some authors have referred to the gut microbiome as "a forgotten organ", because it is involved in several functions that are essential to the host (Clemente *et al.*, 2012). Bacteria in the gut microbiome ferment indigestible food components, modulate the host's energy intake and the assimilation of nutrients, and synthesize certain vitamins and bioactive compounds that are key to human health – all thanks to a collection of enzymes not otherwise encoded in our genes. They also modify other ingested exogenous substances such as medicines and other chemicals.

The intestinal microbiome also contributes to maintaining the integrity of the gut epithelial barrier. Through competition for space and nutrients, the microbiome is the first line of defence against pathogens, and it plays a fundamental role in the training and functioning of the host's immune system (Belkaid and Hand, 2014). Furthermore, when absorbed into the bloodstream, microbial metabolites – either diet-dependent or diet-independent – can act on other parts of the body, modulating several host functions. These include glucose and lipid metabolism, appetite and food intake, systemic immunity, bone metabolism, and even lung physiology (Fan and Pedersen, 2021). The gut microbiome is also an important partner in the communication between the central nervous system and the gut (i.e. the gut–brain axis), and is involved in brain health (Cryan *et al.*, 2019).

2.2 Disturbances and connections with nutrition and health

General features of disease-associated microbiomes

Because the gut microbiome plays such a pleiotropic and important role in human physiology, much research has focused on whether changes in the gut microbiome and the human body could lead to disease. In humans, comparisons of microbiome samples from sick and healthy individuals have allowed for the description of changes associated with diseases.

Only a few chronic diseases have thus far been associated with the presence of "pathobionts" (specific microorganisms of the microbiota with pathogenic potential, associated with chronic inflammatory conditions) – the best example being Helicobacter pylori, which is involved in duodenal ulceration and gastric cancers (Peek and Blaser, 2002). Data also suggest that pathobionts may contribute to obesity and non-alcoholic fatty liver disease (NAFLD) (Fei *et al.*, 2020; Fei and Zhao, 2013). However, most chronic pathologies are associated with more complex perturbations of the microbial population, in combination with other determinants. Since the definition

of a "healthy microbiome" is still a topic of intense discussion, the critical elements of dysbiosis related to health are also subject to controversy.

Nonetheless, most microbiome scientists agree on several features that characterize most disease-associated microbiomes. **Features responsible for dysbiosis include the following** (Duvallet *et al.*, 2017; Petersen and Round, 2014; Wilkins, Monga and Miller, 2019)(see also Figure 2):

i. An overall loss of diversity (taxonomic and/or functional).

ii. A loss or reduction of so-called beneficial bacteria, among which fibre-degrading bacteria are key. This can lead to a decrease in the production of metabolites with anti-inflammatory action, such as short-chain fatty acids (SCFAs).

iii. A higher proportion of potential pathogens, such as members of the phylum Proteobacteria, often associated with increased low-grade inflammation.

The type and amplitude of the perturbations are variable between pathologies, but at least one of these three features of dysbiosis is associated, in humans, with pathological conditions such as obesity, diabetes, cardiovascular diseases (CVDs), colorectal cancer, coeliac disease and food allergies, as well as with asthma, autoimmune diseases, and neurological diseases such as Parkinson's and Alzheimer's (Alcazar *et al.*, 2022; Borges-Canha *et al.*, 2015; Nance *et al.*, 2020; Sun and Shen, 2018; Trøseid *et al.*, 2020; Valitutti, Cucchiara and Fasano, 2019; Zhao, 2013; Zhuang *et al.*, 2020). For child undernutrition, several studies in Bangladesh and Malawi identified differences when comparing the microbiomes of healthy children to those of undernourished children suffering from kwashiorkor – a form of severe acute malnutrition (SAM) (Blanton *et al.*, 2016a; Smith *et al.*, 2013; Subramanian *et al.*, 2014) – or from environmental enteric dysfunction (Chen *et al.*, 2020a). In cases of undernutrition, and SAM in particular, the gut microbiome is mainly characterized by an abnormal maturation (Subramanian *et al.*, 2014), and in some cases by enrichment in bacterial pathobionts (Wagner *et al.*, 2016) or different protozoan and fungal communities (Popovic *et al.*, 2021).

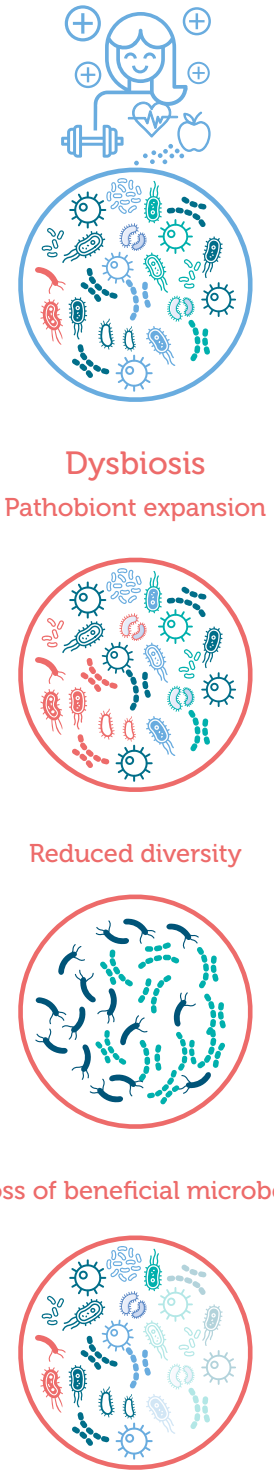

Figure 2. Features of disease-associated microbiomes

Source: Adapted from **Petersen, C. & Round, J.L.** 2014. Defining dysbiosis and its influence on host immunity and disease. Cellular Microbiology, 16(7): 1024–1033. https://doi.org/10.1111/cmi.12308

The three features of disease-associated microbiomes are also associated with diverse detrimental physiological changes for the host that are common to several NCDs; these include increased intestinal permeability associated with inflammation, dysregulation of the immune system, and impairment of the host metabolism (for example, in terms of cholesterol and insulin) (Fan and Pedersen, 2021). In a few cases, mechanistic insight has been identified. For instance, some of the microbiome's effects on the host are mediated by microbial metabolites, and some pathological states are associated with a specific lack of beneficial metabolites, or an excess of detrimental metabolites (Li *et al.*, 2022). In addition, some of the metabolites are produced from the metabolization of dietary compounds (i.e. trimethylamine N-oxide [TMAO], SCFAs and p-cresol) (Fan and Pedersen, 2021), suggesting that the microbiome may mediate some of the effects of the diet on health outcomes. Overall however, more data are needed to elucidate the mechanistic underpinnings of such associations, and to develop potential microbiome-based biomarkers for diagnostics and therapeutic strategies (Wirbel *et al.*, 2019).

From association to causality: What is the evidence?

Most microbiome studies are observational, and do not allow for the determination of whether changes in the microbiome are a consequence (e.g. when changes in the physiological parameters of the host have a secondary influence on the microbial population), or if they play a causal role in the pathology. Causality is typically evaluated by using germ-free animal models (i.e. having no microbiome) and faecal microbiota transplantations (FMTs), or through analytical approaches such as Mendelian randomization (Fan and Pedersen, 2021; Walter *et al.*, 2020). In some studies, disease phenotypes were transferred from animals or humans suffering from chronic conditions, by FMT, to healthy subjects. This has provided some evidence of a causal relationship between a dysbiotic gut microbiome and host disease. **Converging data from animal models suggest that specific changes in microbiome composition and function could play a causal role in diseases such as NAFLD** (Chiu *et al.*, 2017; Le Roy *et al.*, 2019) and **type 2 diabetes** (Liu *et al.*, 2020a), **allergies** (Feehley *et al.*, 2019), **and obesity** (Ridaura *et al.*, 2013; Turnbaugh *et al.*, 2009), **as well as undernutrition** (Blanton *et al.*, 2016a; Chen *et al.*, 2020a; Smith *et al.*, 2013; Wagner *et al.*, 2016).

For obvious technical and ethical reasons, causality is more difficult to prove in humans. There are some conditions however, for which data from human studies also report microbiome disturbances before disease diagnosis or aggravation (Kostic *et al.*, 2015; Stokholm *et al.*, 2018). This temporality is one of several elements that can support causal inferences. Mendelian randomization studies in humans also suggest a causal role for ulcerative colitis (Kurilshikov *et al.*, 2021). Randomized controlled trials (RCTs) in humans, using FMTs from healthy donors to patients, have shown encouraging results – including the reduction of symptoms for type 1 diabetes (de Groot *et al.*, 2021) and ulcerative colitis (Costello *et al.*, 2017; Kedia *et al.*, 2022), decreased fat accumulation in the liver for patients with NAFLD (Craven *et al.*, 2020; Xue *et al.*, 2022), and improved insulin sensitivity (Kootte *et al.*, 2017; Mocanu *et al.*, 2021; Wu *et al.*, 2023). Studies on obesity however, have shown inconsistent results (Ghorbani *et al.*, 2023; Leong *et al.*, 2020).

2

To further elucidate potential causal pathways in human clinical trials, FMTs of human microbiomes pre- and post-intervention have been tested in animal models. Findings provide insights into potential pathways for diet-related modulations of the gut microbiome and improved health outcomes in the context of child undernutrition (Barratt *et al.*, 2022; Charbonneau *et al.*, 2016; Chen *et al.*, 2021; Gehrig *et al.*, 2019; Kamil *et al.*, 2022), childhood obesity (Zhang *et al.*, 2015) and type 2 diabetes (Zhao *et al.*, 2018), and NAFLD (Ni *et al.*, 2023).

However, additional data (through RCTs in humans) are needed, as it remains to be determined whether – and to what extent – the gut microbiome contributes to disease initiation in each context (e.g. form of malnutrition, disease, age group and geography), and the strength of these relationships as compared to other causal factors. Importantly, the gut microbiome may modify the response to treatment for some health issues (e.g. cancer therapy) (Routy *et al.*, 2018). In other cases, despite significant correlations, it is plausible that gut microbiome dysbiosis may contribute minimally or not at all to disease development, or that it may only be a consequence of the disease (Walter *et al.*, 2020).

Better characterization of the interconnections between the gut microbiome and human health are thus required. This in turn requires and relies on a greater understanding of the elements that shape the gut microbiome, including its development, maturation and maintenance.

3

Influencing factors with potential health impacts: Current state of evidence

The microbiome is shaped by various factors, including genetics, age, sex, geography, diet, mode of birth, medication and lifestyle (Manor *et al.*, 2020; Tap *et al.*, 2023), with environmental factors generally playing a larger role than host genetics (Rothschild *et al.*, 2018).

Humans have co-evolved with a core microbiome that has come to be essential to their health. Numerous studies of the gut microbiome in different populations around the world have identified perturbations in the symbiotic relationship between humans and their microbiome; **these perturbations have followed the gradual transition from a traditional to an industrialized/urbanized lifestyle** (Olm *et al.*, 2022; Smits *et al.*, 2017). For example, the microbiome profiles of rural populations with traditional farming practices present an intermediate state between the microbiomes of hunter-gatherers, and those of individuals living in urbanized environments (Jha *et al.*, 2018; Smits *et al.*, 2017). The transition to an urban lifestyle leads to a rapid and significant reduction in bacterial diversity, a reduction or complete loss of certain genera, lower production of certain SCFAs, and an increase in the richness and abundance of antimicrobial resistance genes (Carter *et al.*, 2023; Smits *et al.*, 2017; Sonnenburg and Sonnenburg, 2019). These changes correlate with a higher risk of NCDs in humans, and are consistent with highly controlled experiments and mechanistic findings in animal models.

As variations of the hygiene hypothesis, the **"old friends"** (Rook, Lowry and Raison, 2013) and **"missing microbes"** (Blaser, 2017) hypotheses attempt to connect different environmental factors to human health. These theories propose that several factors – including the nutrition transition towards a so-called "Western diet" (characterized

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by high sugar, high fat and low fibre content), improved sanitation, widespread use of antimicrobials, and the dwindling of direct contact with the natural environment (including soil, plants and animals) – have collectively led to drastic changes in the human microbiome. These changes may in turn result in the impairment of human physiological functions – including those related to the immune system and metabolism – which are hypothesized to be among the drivers in the rise of NCDs.

Exposure to an urbanized lifestyle in early life seems to have profound consequences for health (Bach, 2021; Borowitz, 2023). Indeed, adults who migrate from an LMIC/rural environment to an HIC/urban environment retain higher levels of microbial diversity, and are less prone to immune disorders such as allergies, asthma, type 1 diabetes and inflammatory bowel disease (IBD) (Bach, 2021; Blaser, 2017; Borowitz, 2023). However, the children of those immigrants – or those who immigrate at younger ages – tend to have less diverse microbiomes and higher rates of obesity and NCDs, similar to native residents (Vangay *et al.,* 2018).

Subsequent sections of this paper focus on various factors and their effect on the microbiome – including early life events, diet, and exogenous compounds carried by food. In addition, they explore the potential of the gut microbiome to mediate some of the effects of these factors on health.

3.1 The first 1000 days: A window of opportunity

The first 1000 days of life (from conception to the child's second birthday) are a critical and unique window of opportunity for the initial acquisition of a child's gut microbiome. This begins with vertical transmission of the microbiome from the mother (and is thus dependent on her own microbiome), followed by its maturation to an adult-like composition around the age of three years. Because the gut microbiome influences many host functions (including the digestive, immunological and neurological), it is thought to play a major role in child development (Gensollen *et al.*, 2016). As such, it is essential to understand the various factors that influence microbiome acquisition and development during this time (see **Figure 3**).

During pregnancy, the maternal microbiome mediates some of the effects of maternal health and nutrition on child development (McDonald and McCoy, 2019). Animal studies have shown that the maternal microbiome secretes metabolites that are absorbed into circulation; when they reach the foetus, these metabolites have the potential to impact its development *in utero* (Kimura *et al.*, 2020; Vuong *et al.*, 2020). In addition, the maternal microbiome undergoes some vertical transmission to the child at birth, enabling a direct impact on the infant throughout early life development.

The **dietary choices** of a pregnant woman impact both maternal and child gut microbiome and health (Calatayud, Koren and Collado, 2019), with the intake of fats, liposoluble vitamins and fibres showing the largest correlations (Maher *et al.*, 2020). Both high-fat and low-fibre diets reduce microbial diversity (Maher *et al.*, 2020). In animal models, it was found that when three generations of mice were fed a low-fibre diet, bacterial diversity in offspring was lost and could not be recovered, even after a return to a high-fibre diet (Sonnenburg *et al.*, 2016). Such changes in the offspring microbiome may be correlated with detrimental health outcomes. For example, in an animal model, low maternal fibre intake increases the risk of metabolic syndrome, obesity, cognitive dysfunction, systemic inflammation, asthma and food allergies in offspring, through well-described mechanisms involving the gut microbiome – among other factors (Gray *et al.*, 2017; Kimura *et al.*, 2020; Liu *et al.*, 2021a, 2021b; Thorburn *et al.*, 2015). In contrast, high-fibre intake in pregnant mice has been shown to induce microbial SCFA production by the maternal microbiome. The SCFAs reach the foetus via maternal circulation, improving foetal glucose homeostasis while also reducing the risk of offspring obesity (Kimura *et al.*, 2020). In rats, high maternal consumption of fructose was shown to affect the offspring's microbiome, and is associated with a higher risk of hypertension (Hsu *et al.*, 2018). In humans, high maternal consumption of artificially sweetened beverages is associated with some changes to the child's microbiome, and is correlated with a higher risk of increased body mass index (BMI) (Laforest-Lapointe *et al.*, 2021). And overall, the quality of the maternal diet correlates with positive features in the gut microbiome of both mother and child.

Maternal health conditions such as undernutrition, obesity, IBDs, excessive weight gain and gestational diabetes change the maternal microbiome (toward dysbiosis), and some of these microbial features may be transmitted to the infant. When the microbiomes of offspring from mothers with obesity or IBDs were transferred to germ-free mice, they induced increased weight gain, inflammation and phenotypes associated with NAFLD (Soderborg *et al.*, 2018; Tun *et al.*, 2018). Similarly, germ-free mice with microbiome transplants from a stunted child acquired the stunted phenotype, and the phenotype was transmitted from the dams to their offspring (Wagner *et al.*, 2016).

Medical practices, such as antibiotic treatments and caesarean sections or C-sections, have consequences for the infant gut microbiome (Bokulich et al., 2016; McDonnell *et al.*, 2021; Schulfer and Blaser, 2015). For example, the microbiomes of babies delivered by C-section are more influenced by microorganisms from maternal skin and the hospital environment than vaginally delivered babies (Shao *et al.*, 2019). There is also strong evidence that antibiotic exposure early in life has consequences on child microbiome development. For example, even after accounting for other risk factors, antibiotic treatments received during the neonatal period induced microbiome changes associated with impaired growth, whereas antibiotics received after the neonatal period (up to 6 years of age) led to microbiome changes correlating with a higher BMI (Uzan-Yulzari *et al.*, 2021).

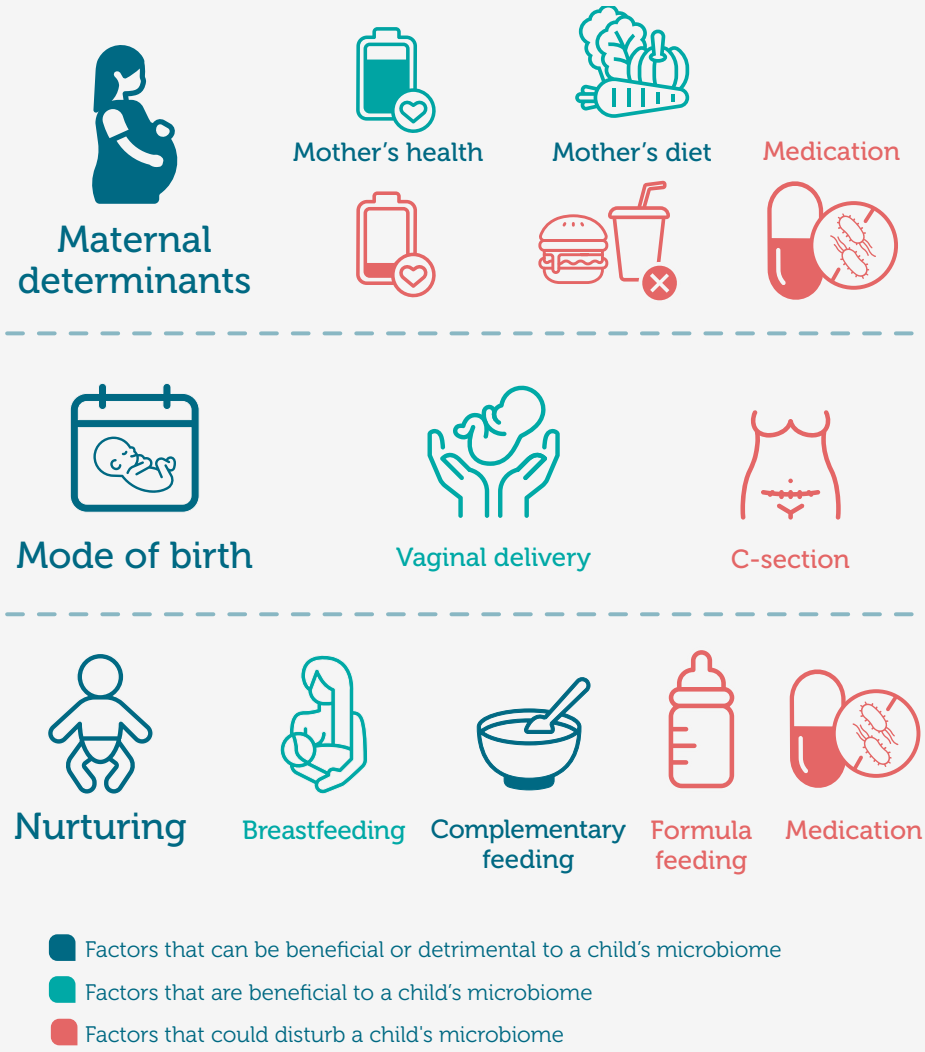

Figure 3.
Main factors influencing the child's microbiome

Source: Authors' own elaboration.

Evidence suggests that microbes implanted in the infant gut early in life may last for months or even years, and may potentially play an important role in the development of the immune system and its function (Bittinger *et al.*, 2020; Gensollen *et al.*, 2016).


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After the mode of birth, diet is the strongest factor in determining infant microbiome maturation, and the beneficial effects of breastfeeding in particular are well documented – both for maternal and child health (Chowdhury *et al.*, 2015; Victora *et al.*, 2016). For example, breastfeeding is associated with a lower risk of obesity, type 2 diabetes, asthma and CVD risk – and the gut microbiome may contribute to this effect – whereas formula milk is associated with increased risk for overweight and some NCDs (Forbes *et al.*, 2018). The extent to which some of these benefits may be partially mediated through the microbiome is an important area of evolving evidence. Breastfed and formula-fed babies have different microbiomes (Stewart *et al.*, 2018), suggesting that breastmilk may strongly shape the microbiome. Breastmilk is also rich in specific elements such as antimicrobial factors, bacteria (i.e. the human milk microbiome) and human milk oligosaccharides (HMOs). HMOs prevent pathogen attachment in infant mucosal surfaces, thus reducing the risk of viral, bacterial and protozoan infections, while also promoting the growth of beneficial Bifidobacterium species (Cheng *et al.*, 2021). Exclusive breastfeeding and breastfeeding for a longer period can increase these beneficial effects, and may at least partially restore the microbiome of infants born by C-section (Liu *et al.*, 2019a). Complementary foods also contribute to compositional and functional changes, and to maturation of the infant microbiome (Laursen, 2021). Their impact is influenced by several factors, including early feeding practices (breastmilk vs formula), infant age, and the type of complementary food. For formula-fed infants, the introduction of solid food induces more changes than in exclusively breastfed infants (Baumann-Dudenhoeffer *et al.*, 2018; Forbes *et al.*, 2018; Thompson *et al.*, 2015), as well as higher dietary diversity, increased alpha-diversity, and a more stable gut microbiome (Homann *et al.*, 2021). Overall, available data support the World Health Organization (WHO) recommendation encouraging 6 months of exclusive breastfeeding for the development of a health-promoting microbiome, but more data are needed on the effects of specific complementary foods.

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In general, long-term prospective studies on mothers and children are needed to clearly demonstrate the impact of microbiome development on child health, but some evidence already suggests that **perturbations in the acquisition and maturation of the child microbiome may be implicated in the well-documented relationships between the first 1000 days and the development of undernutrition in early life, as well as obesity and diabetes** in later life (Fontaine *et al.*, 2023; Robertson *et al.*, 2019).

3.2 Diet as a major modulator of microbiome composition and functions

The relationship between diet, nutritional status, and a number of human health outcomes is well established. While a number of these effects are direct and well documented, new evidence suggests that some diet–health relationships may be mediated by the gut microbiome. Throughout life, diet is among the most important environmental contributors to shaping the human gut microbiome.

When we eat, we also feed our gut microbiome. Food can directly interact with microorganisms to either promote or inhibit their growth. The capability to extract energy from specific dietary components provides a direct competitive advantage to selected members of the gut microbial community, making them more capable of proliferating (Kolodziejczyk, Zheng and Elinav, 2019). Some substances may also have adverse effects on bacterial populations. The diet of the host therefore affects not only the relative abundance of various gut bacteria, but also their growth kinetics and gene expression (Zeng *et al.*, 2022).


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In turn, the gut microbiome metabolism transforms some dietary components, changing their availability for the host. Multiple microbial metabolites are produced in these transformations (Kolodziejczyk, Zheng and Elinav, 2019). Many are still unknown, but those that have been studied in detail have been shown to have a strong impact on human health (Delzenne *et al.*, 2020). Dietary interventions in animal models and humans (through RCTs) have helped to elucidate different diet–microbiome–health connections. Some studies have focused on specific nutrients and dietary components, while others have assessed dietary patterns that have already shown associations with health outcomes (e.g. high-fat diets, diets high in highly processed foods, and the Mediterranean diet). Some dietary compounds, such as fibres and phytonutrients, are more studied as they are known to be specifically metabolized by microorganisms (such as fermentable fibres) (Kolodziejczyk, Zheng and Elinav, 2019). A vast majority of studies are observational (i.e. they assess associations the microbiome may have with health status), but some have used experimental designs that may elucidate potential biological mechanisms; these include germ-free animal models, microbiome depletion due to antibiotics, specific statistical approaches and frameworks such as mediation analysis, and FMT (Shoer *et al.*, 2023).

Fibres

Complex carbohydrates, and in particular fermentable dietary fibres (most of which are soluble, with some exceptions), are defined as microbiota-accessible carbohydrates (MACs). If metabolized by the gut microbiome, MACs play a fundamental role in its modulation (Makki *et al.*, 2018). Indeed, some dietary fibres are minimally digested in the upper human digestive system and go on to reach the colon, where they feed diverse fibre-degrading bacteria. Fibres are mostly found in plant foods such as fruits, vegetables, legumes, nuts and whole grains.

The fermentation of these fibres produces SCFA metabolites – including butyrate – which play important roles in maintaining intestinal barrier functions, gut–brain communication, and protection against inflammation and carcinogenesis (Koh *et al.*, 2016). Several fermentable dietary fibres such as inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS) and resistant starch are classified as prebiotics (Gibson *et al.*, 2017). As defined by the International Scientific Association for Probiotics and Prebiotics (ISAPP), a prebiotic is a "substrate that is selectively utilized by host microorganisms conferring a health benefit" (Gibson *et al.*, 2017, p. 3). However, not all fibres are prebiotics, and some non-fibre components (such as phenolics and phytochemicals) are also classified as prebiotics (Gibson *et al.*, 2017).

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Based on numerous *in vivo* studies and meta-analysis in both animals and humans (see for examples Jefferson and Adolphus, 2019; Sawicki *et al.*, 2017; So *et al.*, 2018), diets high in dietary fibres are associated with positive changes in the microbiome and health, and dietary fibre is associated with decreased mortality risk (Kim and Je, 2014; Yang *et al.*, 2015). However, some inconsistencies and gaps in the evidence remain to be addressed. Importantly, study designs can be improved to elucidate the exposure (in terms of quantity, diversity, type and origin [i.e. whether purified or in the food matrix] of fibres), the duration and timing of exposure, the baseline microbiomes of subjects, and other considerations.

The quantity of fibre intake is important, as low-fibre diets (less than 15 g/day) are associated with a higher risk of several NCDs (Reynolds *et al.*, 2019), and are correlated with negative microbiome disturbance. These include slightly lower diversity and higher relative abundance of Proteobacteria, less SCFA-producing bacteria, and lower levels of SCFAs (Makki *et al.*, 2018; Vinelli *et al.*, 2022). A lack of dietary fibre also leads to a rapid increase in the abundance of bacteria degrading the mucus layer of the intestinal epithelium, which is the first line of defence against pathogens (Desai *et al.*, 2016). Moreover, it may shift the microbial metabolism towards the utilization of less favourable substrates like amino acids, and increase the production of potentially detrimental cytotoxic and pro-inflammatory metabolites (Makki *et al.*, 2018). These microbial changes have been associated with multiple diseases including CVDs, diabetes, coeliac disease, colorectal cancer, allergies and asthma (Alcazar *et al.*, 2022; Borges-Canha *et al.*, 2015; Fan and Pedersen, 2021; Nance *et al.*, 2020; Qin *et al.*, 2012; Trøseid *et al.*, 2020).

Increasing fibre consumption (up to 50 g/day) among consumers of low-fibre diets was shown to improve health-promoting microbiome functions in both animal and human studies (So *et al.*, 2018). High-fibre diets modulated the expression of numerous microbiota metabolic pathways such as glycan metabolism, with genes encoding carbohydrate-active enzymes active on fibres or host glycans, and generally increased SCFAs in stool or plasma – in particular butyrate (Koh *et al.*, 2016).

Importantly, the **type and source of fibres** may change the microbial dynamics (Makki *et al.*, 2018). Consumption of whole grains, intact cereals, fruits and vegetables tend to increase diversity (Jefferson and Adolphus, 2019; Mcdonald *et al.*, 2018). Fibres as a class of molecules (i.e. dietary plant polysaccharides) have high structural complexity, with estimated thousands of structural motifs found in the different foods – primarily plants – that humans consume (Martens *et al.*, 2014). Each type of differently structured fermentable fibre may modulate discrete sets of bacteria/microbiome functions, based on the encoded enzymes involved in fermentation that are present in the bacterial genomes (Cantu-Jungles *et al.*, 2021; Deehan *et al.*, 2020). Indeed, degradation of these complex carbohydrate structures requires the collaborative activity of different species of bacteria, to fully break down the dietary fibres and produce SCFAs (Cantu-Jungles *et al.*, 2021). Even small structural changes in the fibres (for example, when derived from different sources or extracted in different ways) may have an impact on which microbes can metabolize the structure (Tuncil *et al.*, 2020). Given that SCFAs are common metabolites resulting from the fermentation of fibres by numerous bacteria, other specific metabolites/molecules can be expected to be produced or released from different fibre types, with possible impacts on host physiology (Deehan *et al.*,

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2020; Lancaster *et al.*, 2022). For example, N-methylserotonin is released from orange peel fibres by human gut microbiota members, and this molecule reduces adiposity and alteration in liver glucose metabolism in a mouse model (Han *et al.*, 2022). Instead, data from multiple RCTs (meta-analysis) in humans have shown that prebiotics, usually of the single purified fibre type, tend to favour specific groups of bacteria such as Bifidobacterium (for oligosaccharides, FOS and GOS) and Lactobacillus spp. (for fructans and GOS), but did not always improve diversity (Sawicki *et al.*, 2017; So *et al.*, 2018).

Both the quantity and quality (sources) seem to matter (Vinelli *et al.*, 2022). The vast majority of studies showed multiple beneficial effects of fibres on health, but some studies reported no effect or – in a few cases – negative impact from high intake of purified soluble fibres such as inulin, with some effects being mediated by the gut microbiome when the host already existed in a diseased or inflammatory state. In an IBD mice model, high intakes of inulin (but not pectin) aggravated inflammation, but only when associated with a refined (processed) diet (Singh *et al.*, 2018). In humans, intake of purified inulin (> 30 g) induced inflammation when purified arabinoxylan or a mix of five fibres were associated with beneficial effects (such as the reduction of cholesterol) (Lancaster *et al.*, 2022). These results suggest the importance of the food matrix in which the fibre is contained, as well as the global diet.

Data in human RCTs suggest that gut microbiome fermentation of fibres depends on the baseline microbiome, and in particular on the presence or absence of specific fibre-degrading bacteria. In other words, the gut bacterial community should contain the minimal key species that are able to degrade complex carbohydrates, in order to benefit from high-fibre diets (Healey *et al.*, 2018; Jefferson and Adolphus, 2019; Kovatcheva-Datchary *et al.*, 2015; Makki *et al.*, 2018; Sandberg *et al.*, 2019; Wastyk *et al.*, 2021). For example, a randomized controlled trial demonstrated that participants with regular high dietary fibre intakes had a greater gut microbiota response, and were therefore more likely to benefit from an inulin-type fructan prebiotic than those with low dietary fibre intakes (Healey *et al.*, 2018). A randomized dietary intervention in healthy adults showed that a plant-based, high-fibre diet reduced inflammatory markers in individuals with the most diverse gut microbiomes (Wastyk *et al.*, 2021). Data from the comparison between populations in **industrialized** and **non-industrialized** contexts have shown that a diet rich in carbohydrates (i.e. fibres and plant-derived polysaccharides) usually results in a higher diversity, and is dominated by and enriched in polysaccharide-degrading members, *Prevotella* in particular, with increased SCFA production (Mills *et al.*, 2019a, 2019b; Zhao *et al.*, 2018). Interestingly, several studies have also shown that individuals with high Prevotella-to-Bacteroides ratio have better responses to short-term fibre interventions (Christensen *et al.*, 2019; Hjorth *et al.*, 2018; Roager *et al.*, 2014). Long-term adherence to a high-fibre diet seems to be important to maintain the metabolic capacities of the gut microbiome. At population level, major lifestyle changes associated with rapid urbanization and nutrition transition have usually decreased fibre intake drastically (estimated from 100 g/day in hunter-gatherers to less than 15 g/day in several urban environments); this may lead to the permanent extinction of important microbial taxa capable of fermenting fibres (Carter *et al.*, 2023; Makki *et al.*, 2018; Vangay *et al.*, 2018).

Overall, numerous studies in animals and RCTs in humans suggest that long-term consumption of a diet high in amount and diversity of dietary fibres from different plant-food sources (such as whole grains, fruits, vegetables, nuts and legumes) is likely important to increase bacterial diversity and favour a stable and resilient microbiome with a positive impact on health (such as through the reduction of inflammation and cancer markers, and the improvement of glucose metabolism) (Armet *et al.*, 2022; Deehan *et al.*, 2020; Jefferson and Adolphus, 2019; Mcdonald *et al.*, 2018; O'Keefe *et al.*, 2015; Sawicki *et al.*, 2017; Tap *et al.*, 2015). For example, results from the American Gut Project revealed that higher diversity was observed for people who ate more than 30 plant foods (i.e. major sources of fibre), as compared to people who ate less than 10. Even if the potential effects of phytochemicals are taken into consideration (as discussed elsewhere in this paper), it is not only the quantity of fibre but also the diversity that influences microbiome composition and functionality (Delannoy-Bruno *et al.*, 2021; Healey *et al.*, 2018; Jefferson and Adolphus, 2019; Mcdonald *et al.*, 2018; Thorburn *et al.*, 2015).

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Phytonutrients

Data on microbiomes also support the importance of phytonutrients found in plant foods, in particular polyphenols, which are found in fruits, spices, cocoa products, tea and red wine. The health-promoting properties of polyphenols include anti-inflammation, anti-obesity and anti-hyperglycaemia, and seem to be partially explained by their ability to modulate the gut microbiome (Moorthy, Sundralingam and Palanisamy, 2021). They can be used by certain species of bacteria and favour their growth. And thanks to their antioxidant activity, they may also protect beneficial obligate anaerobic gut bacteria. Moreover, microbial metabolism can convert phytonutrients into bioactive molecules. For example, glucosinolate – a biologically inert molecule found in Brassicaceae vegetables – is converted by the gut microbiome into a bioactive chemopreventive metabolite (Liou *et al.*, 2020). Health-promoting properties have also been observed in the polyphenol quercetin (found in red wine, berries, apples and tea) and may be explained by microbiome-mediated metabolites (Porras *et al.*, 2019; Sankaranarayanan *et al.*, 2021). Multiple FMT studies in animals have identified the mediating role of gut microbiota in the beneficial effects of polyphenols on health; these include resveratrol for hepatic steatosis (Wang *et al.*, 2020), citrus flavonoids for metabolic syndrome (Zeng *et al.*, 2020), hydroxytyrosol (the main component of olive oil) for obesity and insulin resistance (Liu *et al.*, 2019b), and various other polyphenols (Anhê *et al.*, 2019; Liu *et al.*, 2020b; Morissette *et al.*, 2020; Zhu *et al.*, 2020).

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Fats

Some of the most striking examples of the importance of the microbiome in mediating the effect of diet on health involves pioneering experiments demonstrating that germ-free mice were resistant to obesity and insulin resistance induced by a high-fat diet (HFD)(Bäckhed *et al.*, 2007; Rabot *et al.*, 2010). Data suggested that a HFD per se is not sufficient to trigger obesity and associated metabolic disorders, and that the gut microbiome is required to obtain an impact from HFDs. **Since then, numerous studies on animal models and in humans have shown that high-fat diets slightly reduce bacterial diversity and increase the pro-inflammatory state** (increasing lipopolysaccharide-producing bacteria) (Bisanz *et al.*, 2019). However, the results are more nuanced when diverse types of fat were considered. For example, adverse effects seem to be more closely associated with saturated fats (Cândido *et al.*, 2018), whereas polyunsaturated fatty acids (such as omega-3 in particular) increase the production of the anti-inflammatory SCFA butyrate (Costantini *et al.*, 2017). Opposing effects of omega-6 and omega-3 fatty acids on metabolic endotoxemia and low-grade inflammation have also been observed, with omega-3 decreases in inflammation appearing to be microbiome-dependent (Kaliannan *et al.*, 2015).

Studies have also shown that the impact of a cholesterol-rich HFD is microbiota-dependent, while that of a cholesterol-free HFD appears microbiota-independent (Kübeck *et al.*, 2016). In addition, recent data show that specific gut microbial populations can reduce serum cholesterol, a blood parameter associated with high risk of CVDs (Kenny *et al.*, 2020).

Interestingly, data from mice suggest that HFDs can induce colorectal cancer and food allergies via microbiome alteration, independent of or before the occurrence of obesity (Hussain *et al.*, 2019; Schulz *et al.*, 2014).


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Dietary proteins

Dietary proteins are an important source of amino acids for bacterial protein synthesis, and are also fermented. Protein fermentation releases small amounts of beneficial SCFAs, but also potentially toxic metabolites that can be converted to activated carcinogens by microbial metabolism (Diether and Willing, 2019). Potentially detrimental effects may be associated with the consumption of some animal proteins, such as red meat and processed meat, but not with low-fat or fermented dairy products (FAO, 2023a). Red meat increases the production of trimethylamine N-oxide (TMAO), a metabolite derived from the microbial metabolism of choline and carnitine that has been associated with increased risk of CVDs (atherosclerosis and thrombosis) (Koeth *et al.*, 2013; Zhu *et al.*, 2016). Studies in animals showed that haem (largely contained in red meat) induced a gut microbiome-dependant epithelial hyperproliferation and hyperplasia, potentially leading to colon cancer (Ijssennagger *et al.,* 2015). Data suggest that intakes of protein from plant foods are associated with healthier outcomes for the microbiome and host physiology (Basciani *et al.*, 2020). These effects may be due in part to the high content of fibres and phytonutrients in plant foods.

Micronutrients

Micronutrients also have an impact on gut microbiome composition. For example, certain micronutrient deficiencies alter microbiome diversity, and may favour inflammation (Chen *et al.*, 2020b; Degnan, Taga and Goodman, 2014). Depending on the micronutrient, the gut microbiome can play diverse roles, ranging from producer (i.e. of vitamins K and B12) to competitor (i.e. for iron). In some contexts, iron supplementation may induce adverse outcomes in the microbiome (on bacterial, protozoan and fungal populations) and lead to higher risk of diarrhoea in already vulnerable child populations (Jaeggi *et al.*, 2015; Tang *et al.*, 2017). In clinical trials, supplements containing iron and zinc (Krebs *et al.*, 2013; Popovic *et al.*, 2021), antioxidants such as vitamin E (Tang *et al.*, 2016) and prebiotics (Paganini *et al.*, 2017) showed potential to counteract some of the negative effects of iron supplementation alone on the microbiome and health. Vitamin D supplementation is also associated with positive outcomes on the microbiome (Waterhouse *et al.*, 2019).

Fermented foods

Fermented foods were part of the human ancestral primate diet, and have since been deliberately produced (through controlled fermentation) and integrated into human cultures for millennia (Carrigan *et al.*, 2015; McGovern *et al.*, 2004). The high prevalence of fermented foods across human cultures is likely due to the enhanced food safety and nutritional qualities of such foods (e.g. removal of potentially toxic components, longer shelf life and high micronutrient availability)(Mukherjee *et al.*, 2023). A high consumption of fermented foods is associated with positive microbiome changes and the production of beneficial metabolites (Mukherjee *et al.*, 2023; Taylor *et al.*, 2020). In a controlled intervention study, eating fermented foods was accompanied by a decrease in over 20 inflammatory markers, along with increased microbiome diversity; both changes are likely to benefit long-term health (Wastyk *et al.*, 2021). Modulation of the gut microbiome by fermented foods may typically occur via one of two pathways:

- The impact of nutrients present in fermented foods. For example, the fermentation process may increase polyphenol bioavailability, and some fermented products contain high levels of readily accessible microbial metabolites such as SCFAs (Leeuwendaal *et al.*, 2022).

- The impact of live microorganisms present in some fermented foods. Some of the live bacteria contained in fermented foods – such as yoghurt, kefir, kombucha, sauerkraut and kimchi – may be transferred to the gut microbiome (Manara *et al.*, 2023; Pasolli *et al.*, 2020). While this transfer may be relatively transient, fermented foods appear to exert a durable positive impact on the host's gut community and immune system (Wastyk *et al.*, 2021). Ingestion of a daily dose of food containing live microbes has recently been shown to correlate with positive impacts on health (Hill *et al.*, 2023).


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Highly processed foods

Highly processed foods – often high in energy, fats (particularly saturated and trans fats), free sugars and salt – **are increasingly associated with detrimental health effects** (Monteiro *et al.*, 2018; Rico-Campà *et al.*, 2019; Schnabel *et al.*, 2019). In the NOVA food classification system, highly processed foods are defined as industrial formulations, manufactured from substances that are in turn derived from other foods (e.g. modified starch, hydrogenated oils and protein isolates), and typically involving the addition of food additives such as preservatives, flavours and colours (Monteiro *et al.*, 2019). In humans, large observational studies on healthy adults have shown that food products usually classified as highly processed foods (i.e. ready-cooked meals, sugar-sweetened beverages and processed meats) were associated with lower alpha-diversity (Partula *et al.*, 2019; Zhernakova *et al.*, 2016). Similarly, refined carbohydrates and dietary sugars such as high-fructose syrup are associated with dysbiosis (Beisner *et al.*, 2020). And another study on adults – both healthy and with intestinal diseases – showed that long-term consumption of processed foods (fast food) favoured pro-inflammatory bacterial species (Bolte *et al.*, 2021). Meta-analysis of a highly processed, very low-energy diet showed an overall negative impact on the microbiome, though with some inconsistency (Lane *et al.*, 2020). Because it is a very heterogenous class of products, it is difficult to generalize what components of highly processed foods specifically affect and/or negatively impact the microbiome. It is likely a combination of factors (for example low fibre, highly refined sugar or salt, and high saturated fat contents) that may act synergistically, along with the potential negative effects of one or several of the various food additives (as discussed in section 3.3) present in many highly processed foods (Armet *et al.*, 2022; Partula *et al.*, 2019; Zinöcker and Lindseth, 2018).

Overall diet quality

It is critical to consider the overall quality of the diet. The interactions between various dietary components and the gut microbiome are complex, and while some effects may be synergistic, others may be antagonistic. For example, high fibre or high polyphenol intakes have been shown to counter some of the effects of a diet high in fat or animal protein intake, and its associations with CVDs and colorectal cancer (Diether and Willing, 2019; O'Keefe *et al.*, 2015).

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As another example, several observational studies and RCTs involving both patients and healthy human subjects have shown that adherence to the Mediterranean diet – which is well recognized as a healthy diet – is associated with various positive features in microbiome composition and function that may mediate some of the diet's effect on health (De Filippis *et al.*, 2016; Garcia-Mantrana *et al.*, 2018; Godny *et al.*, 2022; Haro *et al.*, 2016; Meslier *et al.*, 2020; Rinott *et al.*, 2021; Seethaler *et al.*, 2022; Turpin *et al.*, 2022; Wang *et al.*, 2021).

A range of indicators can be used to assess the quality of a diet, each having certain strengths and limitations. They include the Healthy Food Diversity index, which incorporates dietary diversity and food quality; the healthy and unhealthy plant-based diet indexes (hPDI and uPDI), which consider the quality and quantity of plant-based foods; the Healthy Eating Index (HEI), which considers the extent of alignment with dietary guidelines; and the alternate Mediterranean diet score (aMED) (Fung *et al.*, 2005; Gil, de Victoria and Olza, 2015; Guenther *et al.*, 2013; Satija *et al.*, 2017; Vadiveloo *et al.*, 2014). All the indicators are associated with reduced risk of chronic disease in some population contexts. In a large cohort study, Asnicar *et al.* demonstrated strong correlations between microbial composition and the Healthy Food Diversity index, hPDI/uPDI and HEI in both UK and US cohorts, highlighting the relationship between the microbiome and health-associated dietary patterns (2021), as well as the importance of looking beyond nutrients and single foods in diet–microbiome research. Another study found that the HEI explains the most variance and has the strongest association with gut microbiota composition in an industrialized (i.e. UK) context (Bowyer *et al.*, 2018).

The use of validated indexes that assess dietary patterns such as the HEI or the aMED shows potential to improve the comparability of future investigations on the relationship between diet, microbiome and health (Maskarinec and Hullar, 2020). Food and food-group diversity is one of several characteristics of a healthy diet, and diversity among plant foods has been shown to contribute to microbiome diversity and resilience, with benefits for health (Claesson *et al.*, 2012; Johnson *et al.*, 2019; Mcdonald *et al.*, 2018).

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In summary

Strong evidence already exists for the multiple health benefits resulting from the consumption of healthy diets. Microbiome science can provide important explanations for the potential mechanisms through which healthy diets result in positive health impacts. Consistent with existing dietary recommendations, microbiome research reinforces the importance of consuming a **diverse range of plant foods (i.e. fruits, vegetables, nuts, seeds, legumes and tubers**) to maintain a healthy microbial population and to foster microbial diversity. Plant foods are sources of **various types of fibre** and **multiple phytonutrients**. Metabolites derived from the microbial metabolism of plant foods (such as SCFAs produced from fibres) have been shown to be associated with multiple positive impacts on human health (including metabolism, immunity and brain functions). **Fermented foods** are a possible source of live bacteria and/or bioactive molecules that can also positively shape the gut microbiome. And **breastmilk**, as a natural source of both prebiotics (HMOs) and bacteria, **plays an essential role in shaping the infant's microbiome**.

Microbiome science also brings additional insights to nutrition science and practice. It is well known that not everybody responds to a particular diet in the same way, and data demonstrate that individual responses may depend partially on the individual microbiome (Johnson *et al.*, 2019). Finally, in addition to essential nutrients, microbiome science also invites us to consider diet-derived microbial metabolites as essential for health.

3.3 Exogenous compounds in food: Effects and potential health implications

Exogenous compounds may be intentionally introduced in the food chain (i.e. through the use of food additives during food processing), introduced upstream (e.g. at primary production, in the case of veterinary drug and pesticide residues) or inadvertently present in the diet (e.g. as environmental pollutants and industrial contaminants).

As with nutrients, the interactions within the triad of microbiome–chemical–host are multidirectional (Koppel, Rekdal and Balskus, 2017). Compounds present in food can reach the intestine unmodified, or they can be metabolized by the host. These compounds and/or their metabolites can interact with the gut microbiome either directly or indirectly (by changing the gut environment), possibly altering its composition, diversity and activity.

The microbiome can transform ingested compounds, with the possibility of modifying their bioavailability, altering their toxic potential, and activating or deactivating drugs (Koppel, Rekdal and Balskus, 2017). Overall, it is possible that biologically relevant shifts of the microbiome or the microbial metabolites of exogenous compounds may have some degree of impact on the host – either positive or negative.

Specific substances are covered generally by regulatory frameworks at the global level (such as the Codex Alimentarius) and more specifically by policies in many countries, which are informed by risk assessments. Such assessments determine health-based guidance values such as acceptable daily intake (ADI), and are expressed as dose

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levels. The overall risk assessment process may be used as the foundation for establishing regulatory limits such as maximum residue levels or limits (MRLs), and maximum levels (MLs). MRLs and MLs ensure that the concentration of these substances in food items is kept within safe limits, in order to protect consumers from potential health risks in a long-term perspective, and to ensure safe trade as a primary objective.

Given its role in contributing to international food safety governance, the Food and Agriculture Organization of the United Nations (FAO) has reviewed available scientific literature evaluating the effects of veterinary drug residues, pesticide residues and microplastics on the human gut microbiome, as well as their potential implications on human health (FAO, 2023b, 2023c, 2023d). These reviews evaluated the current state of research on these topics, including the quality and reliability of scientific information needed for regulatory science. A review of food additives is in preparation, using the same approach.

Pesticide residues

Most studies on **pesticides** have been conducted at doses that deviate from realistic concentrations found in foods – with levels higher than existing ADIs – and research tends to focus primarily on chlorpyrifos and glyphosate. Although no causality has been established, some authors have hypothesized that chlorpyrifos-induced gut dysbiosis may be responsible for alterations observed in hosts, such as increased risk of inflammatory and metabolic diseases (e.g. diabetes and obesity) (Fang *et al.*, 2018; Liang *et al.*, 2019; Reygner *et al.*, 2016), altered endocrine function (Li *et al.*, 2019), intestinal dysfunction (Joly Condette *et al.*, 2015; Zhao *et al.*, 2016) and neurological disorders (Perez-Fernandez *et al.*, 2020). For glyphosate, rodent studies using doses ranging from 2 to 4 orders of magnitude higher than the estimated ADI have shown that glyphosate-induced microbial alterations with parallel observations in the host included neurobehavioural dysfunction (Aitbali *et al.*, 2018; Dechartres *et al.*, 2019), small intestine inflammation (Tang *et al.*, 2020) and altered liver function (Lozano *et al.*, 2018).

Veterinary drug residues

Studies on **veterinary drugs** have mostly focused on clinically relevant therapeutical doses. Only a few *in vitro* studies relevant to food safety investigated dose-dependent responses for two endpoints: the disruption of the colonization barrier, and changes in the population of resistant bacteria. The information from these studies was used to determine health-based guidance values such as the no observed effect level (NOEL) and the microbiological ADI (FAO, 2023d).


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Caption: Microplastics such as polyethylene terephthalate (PET), polymethyl methacrylate (PMMA), polypropylene (PP), polyethylene (PE) or nylon can contaminate food and beverages and could alter the gut microbiota.

Microplastics

Foods can also act as vehicles for ubiquitous contaminants such as **microplastics**, and studies have shown that microplastics induce alterations in the gut microbiota of all animal models used. Alterations observed after microplastics exposure included altered intestinal structure and function, gut inflammation, and increased oxidative stress in aquatic animals, as well as alterations in lipid and energy metabolism in rodents. However, the scarcity and heterogeneity of experimental design regarding microplastics (both in terms of animal models and in terms of the types, sizes, shapes and doses of microplastics) make it difficult to draw conclusions (FAO, 2023c).

Food additives

Finally, **food additives** comprise a broad group of substances with different chemical natures that are often found in processed and highly processed foods. These include sweeteners, for example, which are one of the most studied food additives. The evaluation of artificial sweeteners (acesulfame potassium, aspartame, cyclamate, neotame, saccharin and sucralose) in rodents, mostly at doses above ADIs, has shown their potential for inducing gut dysbiosis and altering glucose metabolism. However, human interventional studies have shown contradictory results with regard to the effect of non-nutritional sweeteners on the gut microbiome and glucose homeostasis – from minimal to no effect for high-dose saccharin (Serrano *et al.*, 2021), stevia (Singh *et al.*, 2024) or low-dose aspartame and sucralose (Ahmad, Friel and Mackay, 2020), to microbiome- and individual-dependent glycaemic alterations for low doses of saccharin and sucralose (Suez *et al.*, 2022). In both animals and humans, in vitro and in vivo evaluations of the emulsifiers carboxymethylcellulose and polysorbate 80 (tested primarily at the high-end of concentrations permitted for these food additives) showed their ability to disturb the gut microbiota and penetrate the intestinal mucus layer, and their potential involvement in the intestinal inflammation and altered metabolic activities as observed (Chassaing *et al.*, 2015, 2022; Naimi *et al.*, 2021; Rousta *et al.*, 2021).

Overall observations for risk assessment

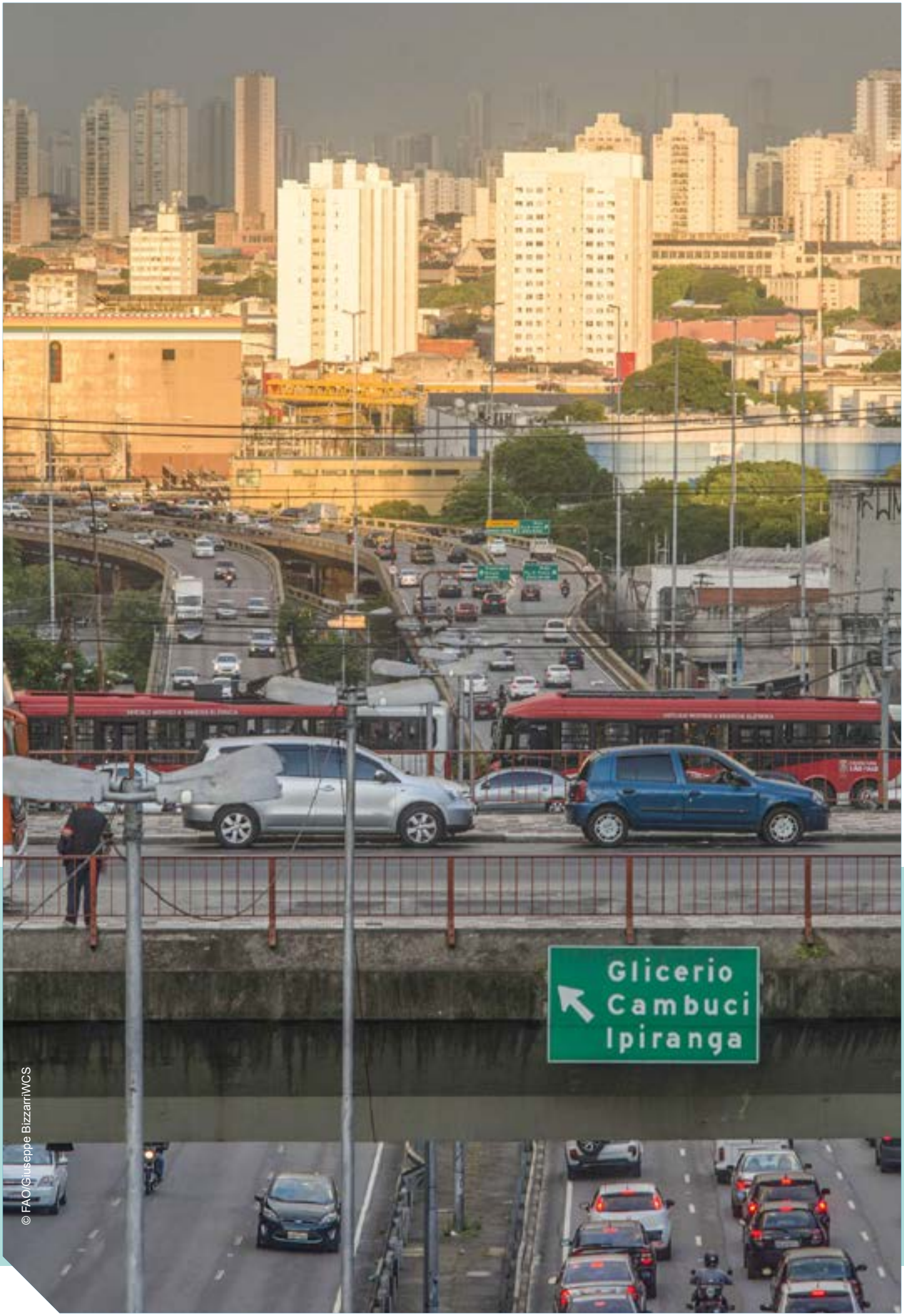
The wide range of **research methodologies used in microbiome studies that test exogenous compounds** – including different study purposes, research questions, study designs, analytical methodologies and statistical approaches – poses challenges in terms of the reproducibility and comparison of research outcomes. Because of these and other critical scientific limitations, such as the low statistical power or biological relevance of findings, some caution is required when approaching the findings and conclusions from many of these studies.

3

From a risk assessment perspective, special attention should be given to **experimental exposure** scenarios, test substances, and doses tested at residual levels. Regarding test substances, these are typically used in their purified form; however, in the case of the pesticide glyphosate, commercial formulations have been evaluated as well, and these showed different effects on the host and microbiome than evaluations using purified substances (Dechartres *et al.*, 2019; Mao *et al.*, 2018). This raises questions regarding the safety of simultaneous exposure to co-formulants in commercial preparations. Microplastic studies have predominantly used commercial pristine particles, which do not resemble weathered particles found in nature. Particle size, shape (fibres and fragments), and surface properties can also influence the impact of microplastics, highlighting the need for suitable reference materials (Toussaint *et al.*, 2019). Moreover, non-food grade additives are often used as test substances, thus introducing uncertainties (such as potential effects from impurities) and making these studies unsuitable for consideration in risk assessments.

In conclusion, to integrate microbiome data in risk assessments, there remains a need for more robust data to better understand the gut microbiome's role in health outcomes after dietary exposure to exogenous compounds. This requires improving scientific rigour in harmonizing study designs, using realistic exposure scenarios and standardized, validated analytical methodologies, and the ability to generate data to comprehensively characterize microbiome alterations and their biological significance. These investigations should not focus solely on microbial composition, but should also delve into microbial functions and impacts on the host. It is necessary to define microbiome-related endpoints, identify and validate sensitive microbiome-related biomarkers, determine their levels of concern, better understand microbiome perturbances of biological relevance, and demonstrate causality and the direction of the host–microbiome relationship.

As such, it may be premature to draw conclusions on the impact of specific exogenous compounds on the gut microbiome and in turn on health. Nevertheless, research developments in this area are well monitored by food safety risk assessment bodies, with a view to greater clarity in the near future (FAO, 2023b, 2023c, 2023d; Merten *et al.*, 2020).



Preventing malnutrition: Implications of current evidence and promising action areas

4

Along with the growing body of evidence on demonstrated associations between the gut microbiome and host health, and of causal linkages in some circumstances, it is also known that the gut microbiome responds more rapidly to lifestyle changes – and particularly to dietary changes – than our own human genome (Sonnenburg and Sonnenburg, 2019). This responsiveness of microbiota to environmental and dietary exposures has potentially crucial consequences. On one hand, for example, industrialization and urbanization have been associated with a rapid loss of microbiome diversity – this endangered diversity needs to be preserved to support human health (Sonnenburg and Sonnenburg, 2019). On the other hand, the same malleability that makes the microbiome a vulnerable aspect of human biology also makes it an important and relatively accessible target for action to improve human health.

There is already a food–drug continuum of action based on microbiome science. In medicine, microbiome science is expected to contribute to the development of early diagnostic tools, and is a new target for therapeutic approaches to treat NCDs and obesity (Doré *et al.*, 2017; Hajjo, Sabbah and Al Bawab, 2022; Sorbara and Pamer, 2022; Su *et al.*, 2022). And from the nutrition side, food and diets provide the basis for an effective and affordable strategy, and may be the safest pathway for modifying the microbiome (see **Figure 4**).

Microbiome-based knowledge strongly supports the importance of healthy diets that follow the well-defined requirements of nutrient adequacy, balance, diversity and moderation – along with safety (FAO/WHO Joint statement of healthy diets, forthcoming). It also highlights the importance of diets with higher and more diversified intakes of plant foods and dietary fibres in particular (even more than

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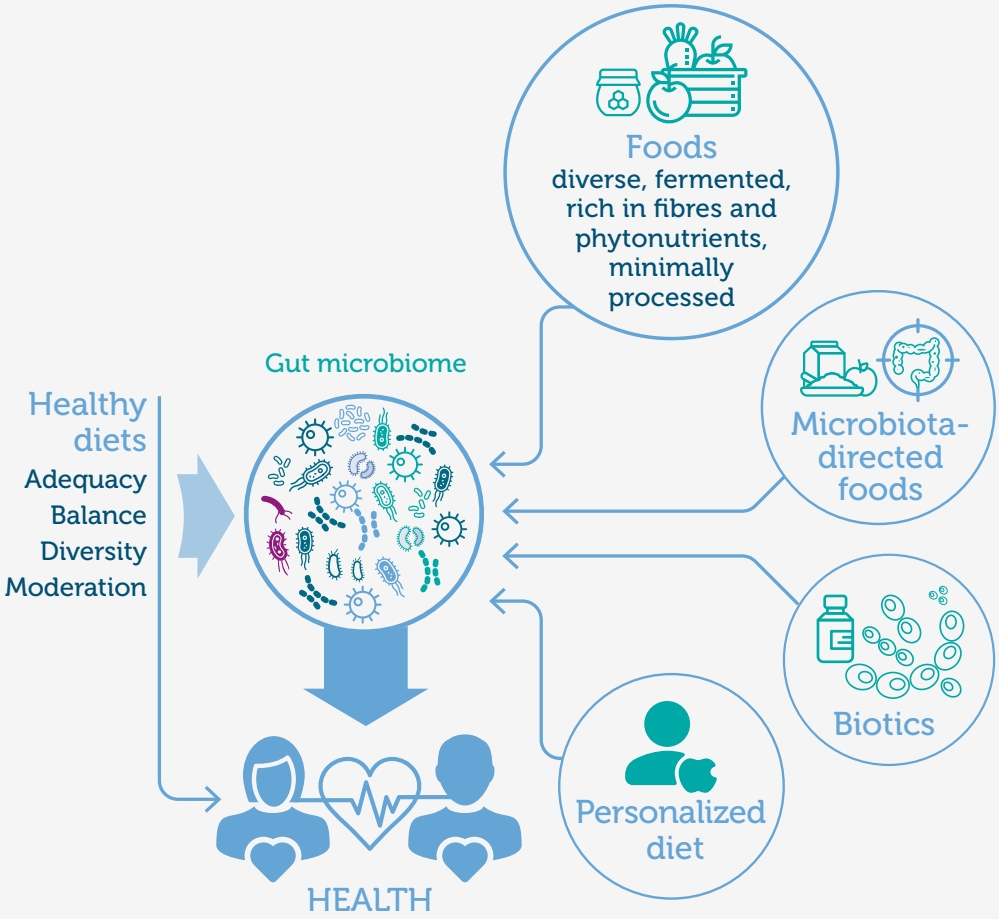
current recommendations; i.e. beyond 30–40 g/day), as well as phytonutrients, minimally processed foods and fermented foods (Mcdonald *et al.*, 2018; Taylor *et al.*, 2020), as these elements appear critical to shaping a healthy and resilient microbiome from a young age. Moreover, maintaining a healthy microbiome may in itself provide an additional element in the prevention of undernutrition, obesity and associated NCDs.

As an example, short-term dietary interventions that integrate these microbiome-supporting elements have shown very encouraging results for managing obesity and type 2 diabetes (Hiel *et al.*, 2020; Zhao *et al.*, 2018). At the same time, other findings suggest that the long-term health of the microbiome may depend on long-term adherence to a healthy and microbiome-supporting diet, and that the increased resilience of the microbiome as a result of short-term interventions may be limited (Bolte *et al.*, 2021; Fragiadakis *et al.*, 2020; Leeming *et al.*, 2019; Yu *et al.*, 2021).

In addition to healthy diets in general, different innovative food-based strategies are being developed to target the microbiome – some of which are specifically designed for particular medical conditions (such as obesity, undernutrition and NCDs). As described in the rest of this section, these include "biotics", microbiota-directed foods and personalized diets (see also Figure 4).

Figure 4. Targeting the gut microbiome to improve health



Notes: Healthy diets contribute directly to nutrition and health outcomes. Some elements of a diet (such as higher diversity of plant foods, higher intakes of fibres and phytonutrients, as well as fermented foods) will also have an impact on health as mediated via the gut microbiome. In specific contexts, complementary approaches targeting the gut microbiome may also improve an individual's health: (i) one or several biotics (probiotics, prebiotics, synbiotics and postbiotics); (ii) microbiota-directed foods; and/or (iii) personalized diets based, among other criteria, on a person's particular microbiome data.

Source: Authors' own elaboration.

4

Spurred by the rapid development of knowledge on the role of the gut microbiome in human health, the food industry is investing heavily in microbiome research and – in some contexts – in the development of innovative food products that target the gut microbiome to offer health benefits. This includes food ingredient and food supplement producers, consumer goods companies and food start-ups, many of whom are already developing specific foods, food complements and personalized diets for particular target groups, to prevent or treat particular chronic conditions (OECD, 2017). The role of these products as part of a healthy diet requires further articulation in dietary recommendations. Further study – and possibly regulation – is also required to ensure that innovative products maintain otherwise healthy nutrient profiles, and that healthy levels of processing are maintained.

4.1 Biotics: Probiotics, prebiotics, synbiotics and postbiotics

The idea of targeting the gut microbial population to improve human health is not new. In 1908, Elie Metchnikoff proposed the probiotic concept of using lactic acid-producing microbes to counter senility (Metchnikoff, 1908). But it was only a century later, in 2001, that a definition of "probiotic" was officially proposed by FAO and WHO.

As defined by Hill *et al.* (2014, p. 507), **probiotics** are "live microorganisms, which when administered in adequate amounts, confer a health benefit on the host". In humans, numerous clinical trials and meta-analysis on probiotics show that the effects are mostly positive for various health issues (e.g. amelioration of anthropometric measures of overweight and obese patients with related metabolic diseases [Perna *et al.*, 2021], reduced risk of diarrhoea in undernourished children [Kambale *et al.*, 2021] and prevention of gestational diabetes [Łagowska *et al.*, 2020]). The paediatric use of probiotics has been shown to be very effective under certain conditions, as an infant's microbiome may be more receptive (Frese *et al.*, 2017). Currently, the main bacteria used as probiotics are *Bifidobacterium* and *Lactobacillus*. However, it is important to acknowledge that probiotic effects are highly strain- and disease-specific (McFarland, Evans and Goldstein, 2018), and are often transient. Because the definition of probiotics implies a health claim, the use of the term "probiotic" is not allowed for most products that are found on the market in most European countries (including those containing some of the bacterial strains that were used in clinical trials).

Next-generation probiotics may be based on novel strains that live naturally in the digestive tract, and are likely to be identified based on a deeper understanding of the human microbiome. Compared to traditional probiotics, they require additional safety characterization and functional analysis, but they hold significant potential to treat NCDs. Before their use as food supplements or live biotherapeutic products (i.e. drugs), proof of concept of their relevance for human health will be required through adequately controlled intervention studies (Langella, Guarner and Martín, 2019).

Postbiotics are usually derived from probiotics, and are defined by Salminen *et al.* as a "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" (2021, p. 1). As a heterogeneous mixture of components, their effect on health may be driven by many different mechanisms

(e.g. by modulating the gut microbiome, enhancing the epithelial barrier function, or modulating the immune system). There are a few clinical trials in humans that show beneficial effects in adults in the context of IBD, cancer, obesity or stress (Salminen *et al.*, 2021). Postbiotics might be an advantageous option compared to probiotics, as they are easier to produce and conserve, and there are fewer safety concerns than with live organisms (which many probiotics contain). Interestingly, in some cases, inactivated probiotics may have more positive impact than live organisms (Plovier *et al.*, 2017), as in the case of *Akkermansia muciniphila*, which was shown to reduce inflammation associated with fat storage and obesity in an RCT in humans (Depommier *et al.*, 2019).

Another way to influence the gut microbiome is to improve the growth and function of specific gut-resident organisms, with **prebiotics**. These refer mostly to specific types of carbohydrates that are naturally present in vegetables, and also include ingredients purified from plants (i.e. purified fibres).

The market is currently dominated by a narrow range of confirmed prebiotic substances – mostly galactans and fructans (e.g. inulin) – which belong to the class of fermentable dietary fibres (i.e. MACs). However, the concept is now being extended to a large group of food components (arabinoxylans, pectins and pectooligosaccharides, some resistant starches, chitin-glucans and polyphenols) that are metabolized by the gut microbiome. Most of the data derived from intervention studies on nutrients with prebiotic properties have been performed with purified compounds that were given as a dietary supplement versus a placebo. Not surprisingly, the foods that are naturally rich in prebiotic dietary fibres (e.g. cereals and root vegetables) are an essential part of healthy diets.

A very large selection of functional food products (Bigliardi and Galati, 2013) **is already enriched with probiotic-type organisms and/or prebiotic carbohydrates.** For example, fermented foods often contain a diverse mix of organisms that, while not investigated individually in controlled studies (as is the case with many bona fide probiotics), are similar in phylogeny and function to known probiotics. Investigations of the microbiome have also resulted in the prebiotic and probiotic enrichment of specific foods for infants. In particular, infant formula and follow-on milks are being reformulated based on improvements in understanding the components of human milk that are known to exert beneficial effects on the infant microbiome and health, including the naturally occurring prebiotics (HMOs) that promote Bifidobacterium species (Salminen *et al.*, 2020).

Most of these new products may not yet be affordable for everyone, particularly in LMICs. **But a few microbiome-based initiatives in Argentina, Bangladesh and Eastern Africa have successfully provided access to foods containing probiotics for many people in the most challenging environments, albeit at a small scale to date.** As part of these initiatives, fermented foods – which are traditionally produced in many countries – were used as vectors, and enriched with easy-to-use sachets of *Lactobacillus* strains (some of which were locally isolated) (Reid *et al.*, 2018). These local, probiotic-enriched fermented foods were produced through a gender-responsive, pro-poor business model, taking into consideration economic needs and gender dynamics across beneficiary communities (Reid *et al.*, 2020).

Pre- and probiotics may also help in developing products to reduce micronutrient deficiencies. For example, the Bill & Melinda Gates Foundation recently funded several projects focused on feeding traditional fermented foods to women of reproductive age in LMICs (Bill & Melinda Gates Foundation, 2020), with one of the primary goals being improved outcomes for infants, specifically in terms of low birth weight and stunting. And possible adverse effects associated with **iron supplementation** in children (e.g. diarrhoea) may be reduced with safer formulations containing prebiotics (Tang *et al.*, 2016) or probiotics.

As observed during the COVID-19 pandemic, risks related to NCDs and infectious diseases may be linked. Data suggest that in obese and diabetic patients, gut microbiome dysbiosis – particularly the overgrowth of opportunistic pathogens – may confer higher susceptibility to severe forms of COVID-19 (Ferreira, Viana and Reis, 2021). Specifically targeting the gut microbiome to mitigate COVID-19 complications is currently being tested in at least ten clinical trials – mostly with probiotics, but also with botanical-based formulas or polyphenols (de Oliveira *et al.*, 2021). However, there is a need for additional studies on how dietary modulation of the microbiome–immune axis influences infectious disease and the vaccination response.

4.2 Microbiota-directed foods

Microbiota-directed foods (MDFs) are a new type of functional food. They have been defined by Barratt *et al.* as foods that operate "by altering the functionality of the gut microbial community, providing substrates for microbial transformation to metabolites necessary for a healthy state, or by acting through a combination of these mechanisms" (2017, p. 135).

MDFs differ from prebiotics, and may represent a larger set of foods composed of a variety of ingredients, including one or more prebiotic components. They may be used as new therapeutic or supplementary foods to combat undernutrition – as in Bangladesh, where MDF prototype formulations were prepared with locally available, affordable, culturally acceptable and commonly consumed complementary foods, and tested in animals and infants (Gehrig *et al.*, 2019). They have also met the well-established nutrient content requirements for children with moderate acute malnutrition (MAM). For example, a three-month RCT of MDF interventions showed better growth outcomes and microbiome repair for treating MAM than a rice and lentil-based, ready-to-use supplementary food (RUSF) (Chen *et al.*, 2021; Mostafa *et al.*, 2020). Indeed, incorporating microbiome considerations in RUSF foods proven for the treatment and prevention of MAM may further enhance their efficacy. This requires further testing however, including in larger populations across different countries and contexts.

In addition, prototypes of multifibre snacks that are specifically designed to impact the microbiome have recently been tested in human trials with encouraging results – especially for overweight and obese patients (Delannoy-Bruno *et al.*, 2021) and subjects at cardiovascular risk (Ranaivo *et al.*, 2022). Other examples of food products specifically designed to target the microbiome in specific populations of type 2 diabetes patients and obese children (though not based on personalized data) have also shown positive results (Zhang *et al.*, 2015; Zhao *et al.*, 2018).

4.3 Personalized diets

Several human clinical trials (on healthy and diabetic patients) have shown that not all individuals respond equally to the same diet, and that the composition of the microbiome before a given dietary intervention can significantly influence the health outcomes (Johnson *et al.*, 2019; Zeevi *et al.*, 2015). These studies may contribute to the understanding of why the impact of nutritional interventions varies among individuals, offering information beyond the data commonly collected as part of epidemiological and clinical studies.

Personalized diets based on microbiome analysis are very promising, and may be particularly relevant for patients suffering from specific conditions like obesity and NCDs. Such dietary interventions have already shown positive results in the context of type 2 diabetes (Zeevi *et al.*, 2015), but they have not yet been proven effective for other health conditions. Additionally, it may be possible to envision strategies to improve health not at the individual level but at the sub-population level, using common microbiome features (among other criteria) as a basis (Blanton *et al.*, 2016b). The current costs and implementation modalities associated with microbiome analysis make personalized diets based on microbiome data inaccessible to the majority of the world's population. But with advances in digital technologies and assessments across different populations, costs are expected to drop, and access is bound to improve.

What's next: making microbiome science and innovation work for nutrition and health

5

Despite significant advances in the understanding of the microbiome's role in human health and its links with all forms of malnutrition, major research and knowledge gaps remain. There is a need to expand and diversify investigations – both in terms of fundamental microbiome research, as well as more applied research aimed at understanding the role that food systems and diets play in shaping the microbiome (and the resulting impact on human health) – while also considering relevant contexts and critical interactions with other environmental considerations.

5.1 Addressing gaps and expanding support for microbiome research

Despite major and rapid advances in microbiome science, several research and knowledge gaps remain in our understanding of the interconnections between diets, the human microbiome and health. Understanding these gaps is critical to addressing them through a range of approaches (as discussed in the rest of this section), and further translating this knowledge into informed and effective actions to improve health. (See also **Figure 5**.)

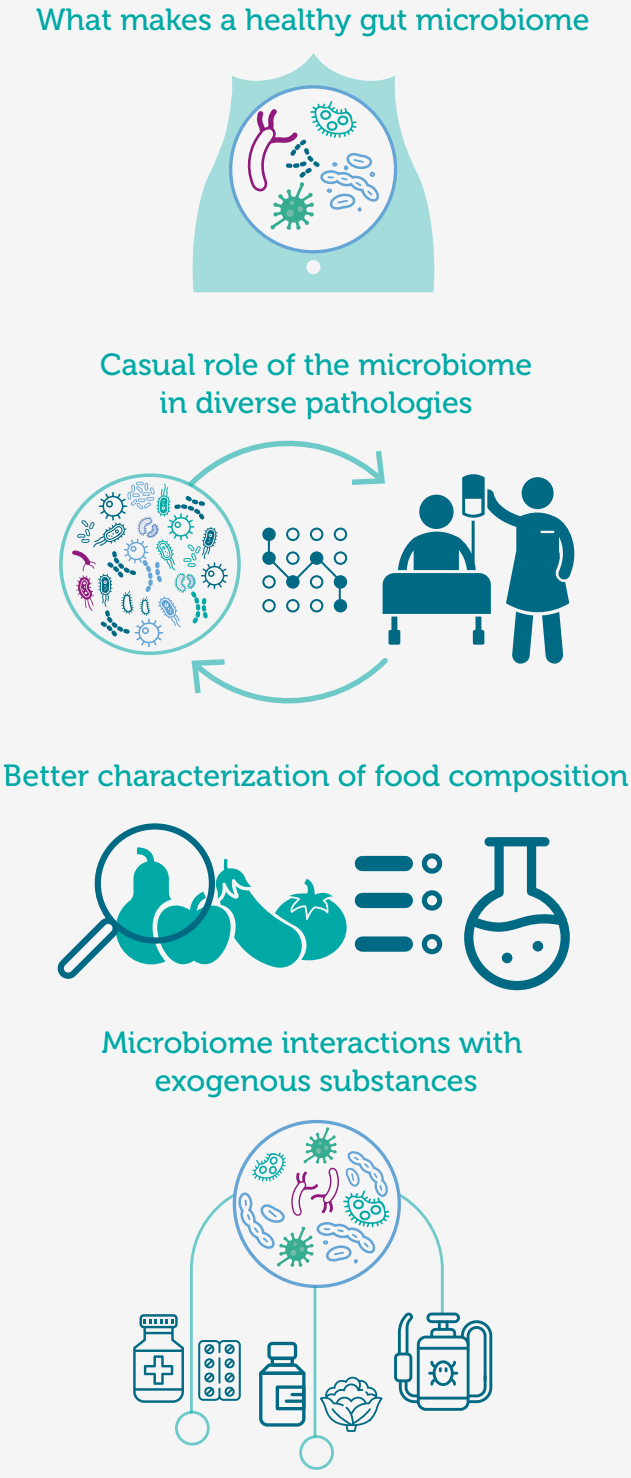
The definition of a healthy gut microbiome – and by implication the definition of dysbiosis – is still a major challenge in the microbiome field. It is now clear that such a definition needs to go beyond a simple taxonomic description at genus level, and should aim for a better characterization not only at species level but especially at functional level (e.g. genes and metabolites). The functional activity analysis will help clarify the connection between specific microbial functions and their effects on the host, thus allowing for a more comprehensive understanding of the microbiome's role in health and disease. Moreover, given that a large number of the gut bacterial species that have co-evolved with humans are disappearing in the context of industrialization, a better understanding of how this vanishing component of human microbial biology relates to modern diseases (such as NCDs) is urgently needed. And in addition to bacteria, there is a vast and understudied diversity of other microorganisms – such as fungi and viruses – that can also affect human physiology and that therefore require consideration. Returning to the need for a definition of dysbiosis, it is also essential to clarify the biological relevance of microbiome-related disturbances in the host, in order to further establish microbiome biomarkers and references for diagnosis and risk assessment.

Microbiome samples from faecal material are usually used as proxies for colon content. However, recent data have indicated discrepancies between faecal microbiota and the microbial communities of the colon (Folz *et al.*, 2023; Shalon *et al.*, 2023), and several studies have also shown the importance of other gut segments such as the small intestine (Chen *et al.*, 2020a; Folz *et al.*, 2023; Tang *et al.*, 2020; Vonaesch *et al.*, 2022). The very recent development of non-invasive tools

– such as an ingestible device that moves through the intestinal tract as part of normal digestion, collecting samples from multiple regions – should help to ensure a more realistic understanding of activities across the microbial community (Folz *et al.*, 2023; Shalon *et al.*, 2023).

Figure 5. Major gaps in understanding and research on the microbiome

Source: Authors' own elaboration.



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A better understanding of the causal role of the microbiome on health is also fundamental. Converging data – using FMTs in animal models, epidemiological studies with Mendelian randomization, and RCTs in humans – have suggested some causal relationships. But overall, it remains difficult to study causal relationships in humans. Establishing causality requires RCTs – supported by long-term prospective cohort studies that use established criteria to assess causal linkages. Establishing the extent to which relationships are causal is fundamental to assessing the contribution of the microbiome to health and disease, and to determining the extent to which it is both justified and feasible to integrate the microbiome in strategies (whether preventive or therapeutic) to support human health and nutrition. Further research should then extend to factors that modulate the gut microbiome, such as diets or exogenous compounds.

With regard to birth-related factors, diets are the most significant – and among the most accessible – factors shaping the gut microbiome. Clear conclusions are already emerging from the literature, but **better characterization of food composition beyond macro- and micronutrients and their interactions with the bacterial community** is strongly needed. Examples include the production of microbial metabolites resulting from food metabolism, and the interactions between the extensive array of dietary fibres and the microbes and genes responsible for their metabolism. Such information has the potential to substantially advance both microbiome and nutrition research, and is essential to better informing both whole-diet and targeted approaches.

Given the broad array of uncharacterized microbial metabolic activities, there is a **need to better understand microbiome interactions with exogenous substances**, and the consequent influence on bioavailability and toxicity. Although challenging, more data on the total exposome and potential "cocktail" effects are also strongly needed, as most people are likely to be exposed to a combination of several substances – as shown for food additives (Chazelas *et al.*, 2021). These studies should also consider host factors that can modulate or alter such interactions. And in terms of risk assessments on the effects of veterinary drug and pesticide residues and microplastics on the microbiome and health, recent publications have discussed a range of specific gaps in great detail (FAO, 2023b, 2023c, 2023d). The rest of this section offers several recommendations to address these gaps across a range of key areas.

Standardization and reporting

Standardization is necessary in order to compare and combine separate studies (meta-analysis), and should be available for each step of microbiome studies, including (i) material sampling, (ii) sequencing, (iii) data analysis, and (iv) data archiving and publication. More than complete standardization of research protocols, the aim is to establish quality control standards at each step. The recently proposed STORMS (Strengthening the Organization and Reporting of Microbiome Studies) checklist may help to add more transparency on methodology choices, and offers significant potential for benefits in studies comparison (Mirzayi *et al.*, 2021).

The International Human Microbiome Consortium (IHMC) has been raising awareness on the importance of sharing data and standards internationally by holding international conferences since 2008. However, there remains a need at and through

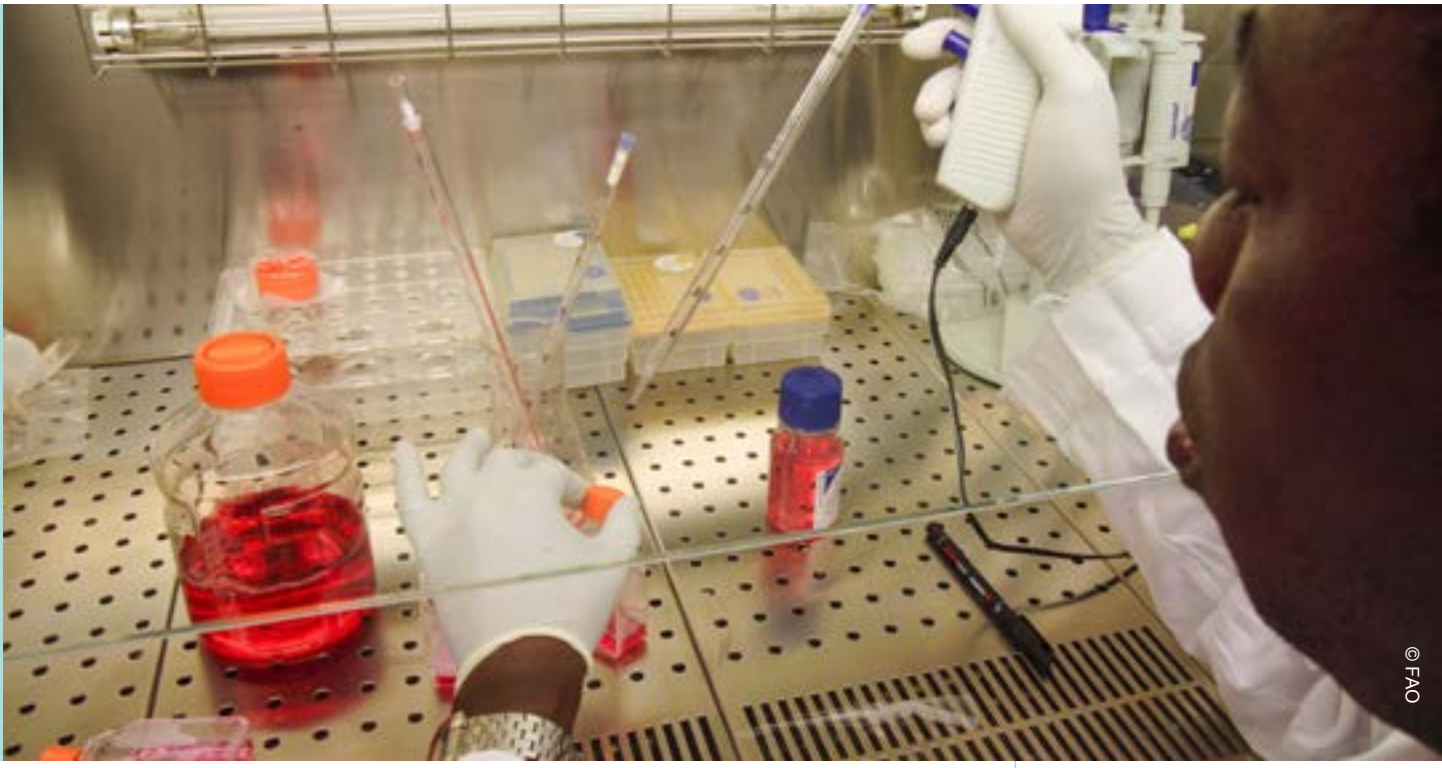
such events, to foster multilateral funding collaborations on microbiome standards and big data. Databases should be accessible across different microbiomes, as well as throughout different countries and continents.

In the context of regulatory frameworks, research methodologies suitable for evaluating specific purposes (such as the evaluation of chemical residues, antimicrobial and colonization resistance, probiotics, nutrients, etc.) should be standardized. Examples include the design of in vivo and in vitro studies suitable for the safety evaluation of regulated substances. Experimental periods should be representative of chronic exposures, and should incorporate several time points for sampling in order to monitor microbiome fluctuations before, during and after treatment, along with associated long-term implications for the host.

Interdisciplinary research

Microbiome research is inherently interdisciplinary and therefore requires collaboration, the integration of skills and the sharing of best practices across many areas.

The nutrition and microbiome fields are deeply interconnected, and could benefit from cross-pollination. To fully capture microbiome–diet–health interconnections, it is essential to better understand what people really eat. This may require better dietary assessment methods in microbiome studies, and a more thorough overall characterization of food composition at the molecular level, especially as studies have shown that microorganisms have the capability to metabolize very specific molecules contained in food – in particular bioactive compounds – and turn them into beneficial metabolites for the human host (e.g. converting glucosinolates from Brassicaceae into bioactive isothiocyanates with antioxidant and anti-inflammatory properties) (Liou *et al.*, 2020). Important advances in the field of food composition may have the potential to characterize exactly those components that are currently



not quantified in our food supply, through the use of evolving "omics" technologies (Ahmed *et al.*, 2022). And advances in analytical chemistry using mass spectrometry provide an additional opportunity to gain unprecedented insights into the biochemical composition of foods (Ahmed *et al.*, 2022). For instance, surprisingly little is known about many of the plant-derived carbohydrate structures that we consume in our diets, and how these vary as a function of growing conditions, cultivars and food processing methods. Integrative approaches coupling food composition analysis with microbiome metagenomics are therefore needed.

As an example, the European FiberTAG project (Neyrinck *et al.*, 2020), which focuses on fibres, proposes to establish a set of biomarkers linking dietary fibre intake and health effects related to gut microbiota. The project also aims to refine the concept and classification of dietary fibre, based on novel biological effects related to interactions between nutrients and gut microbiota. Tools developed through the project may be extended to a larger subset of countries worldwide, providing detailed documentation on dietary habits and the different food products available to various populations. This may help to refine dietary recommendations on dietary fibre intake that consider the rationale of their physiological effects, as linked to interactions with the gut microbiome (Neyrinck *et al.*, 2020). Furthermore, it could inform recommendations for increasing and optimizing dietary fibre intake.

Higher education

Addressing research gaps requires training the current and future workforce to conduct research and product development in the microbiome–nutrition–health field, as well as building capacity to conduct evidence-based outreach with consumers. Microbiome curricula need to be included in undergraduate to postgraduate programmes for various disciplines, including medicine, biology, chemistry, agronomy, engineering, public health and even social science. This will foster interdisciplinarity and promote translational initiatives on microbiome research. Skills in bioinformatics, mathematics, biostatistics, computational science and artificial intelligence are also essential, in order to extract relevant information from big data generated by microbiome studies. However, such skills are not usually taught extensively in biological fields, and closing this educational gap is critical.

Citizen science

Participatory approaches such as citizen science may help to access a very large collection of microbiome samples (from stool, food or the environment), by engaging members of the general public on collaborative projects with professional scientists. Such approaches enable and facilitate initiatives that would otherwise prove impossible in traditional research settings, due to the lack of both human and financial resources. In the case of the gut microbiome, citizen science could help to enable access to a larger range of individuals with different lifestyles in diverse countries – and particularly in LMICs. The Microsetta Initiative, for example, is a research project led by a team at the University of California, San Diego, that aims to recruit thousands of people around the world to map their gut microbiomes. Citizen engagement is also a powerful way to raise public awareness on microbiome research and innovations, and their potential to improve health.

5

Involving low- and middle-income countries

Microbiome science is currently carried out primarily by specialized research centres in HICs. And while different Indigenous Peoples' in LMICs have been the subject of various studies, the involvement of researchers in LMICs is fairly limited. However, if microbiome research is to lead to innovations that apply across the world, it is critical to obtain representative and specific data for each sociogeographical context – including LMICs – and to ensure such contexts can present their own unique and evolving combination of factors in terms of environment, dietary patterns, and nutrition and health outcomes. Expanding the collective knowledge base on the gut microbiome around the world will help to define the diverse characteristics of healthy microbiomes, and clarify aspects of healthy microbiomes that are specific to a given population context. Part of this effort should focus on location-specific diets, their unique composition, and their impact on microbiome and health outcomes.

Capacity development and the involvement of researchers in LMICs are also important priorities in view of the context-specific nutrition and health problems that prevail in these countries. Microbiome science offers significant opportunities for deepening and expanding the impact of nutrition and health strategies in LMICs, for example through the use of various pre-, pro- or synbiotics (possibly in the context of traditional foods and diets); more informed, science-based support for breastfeeding; and MDFs for treating undernutrition (and MAM in particular).

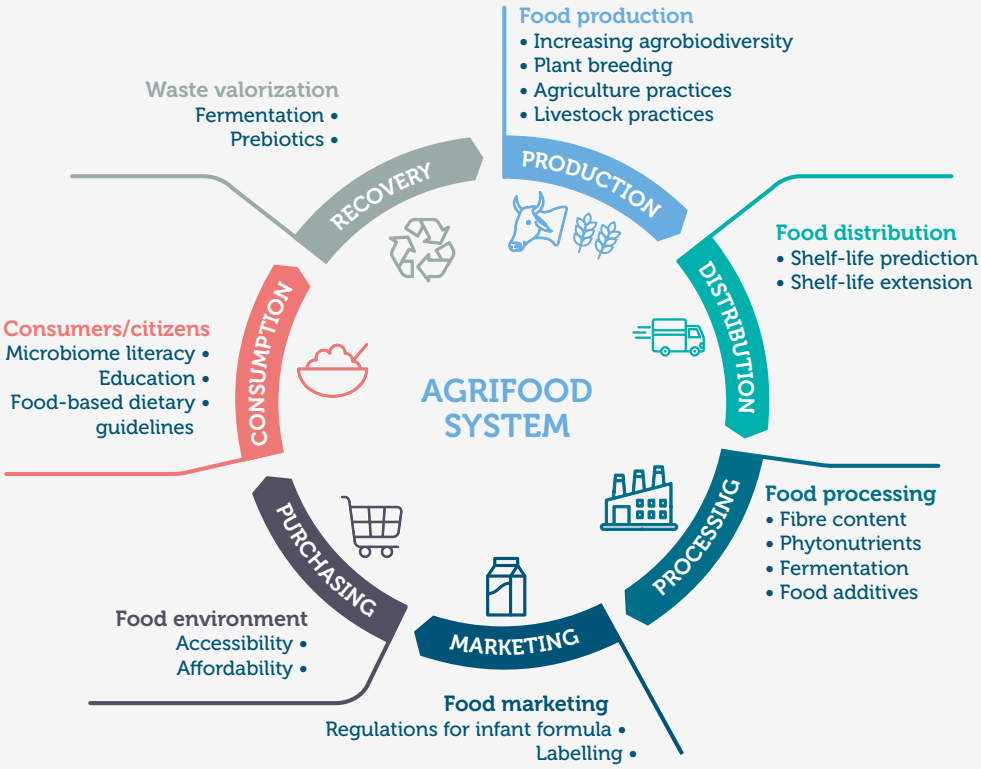
5.2 Implications for agrifood systems

The lifelong adoption of healthy diets that consider the role of the microbiome in nutrition and health has critical potential implications for agrifood systems overall.

A practical example of these implications is offered by the Food4Gut multidisciplinary project, which aimed to better understand how inulin-type prebiotics that are naturally present in vegetables may improve gut microbiota homeostasis and health. The project investigated different step sequences of the food system in a region of Belgium, from the identification of locally produced vegetables with higher inulin content and the effect of cooking on inulin contents, to the development of menus based on the identified vegetables and the effect of the food environment on consumer behaviour toward inulin-rich foods. The data showed that eating locally produced, inulin-rich vegetables drives gut microbiota changes previously shown with "pure" inulin as a dietary supplement, demonstrating the efficacy of a food-based intervention. They also show how the initial gut microbiome characteristics may explain interindividual variability in terms of improving adiposity and behaviour in obese patients (Neyrinck *et al.*, 2021). (See also Figure 6.)

Figure 6. Implications of microbiome science for agrifood systems

Source: Authors' own elaboration.



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Consumers and citizens

Information on the role of the microbiome in nutrition and health must be made available to consumers and citizens in ways that, while based on scientific evidence, are clear and understandable to non-scientists.

Understanding how microbiomes impact people's lives on a daily basis can support consumers in making better, more informed decisions – both individually and collectively – on health and nutrition, and can lead to a greater acceptance of microbiome innovations, including in other sectors such as agriculture. Several new products related to the microbiome are already on the market – in some cases with unclear health claims or marketing (as for some probiotics). The public should be correctly informed about the potential of microbiome-supporting foods, and should also be protected from potential hype and misleading information in this field. This will require concerted action by diverse responsible actors – the research community, food and healthcare professionals, the private sector, regulatory agencies, the media and policymakers.

Through **food-based dietary guidelines (FBDGs)**, governments provide advice to the public on locally appropriate foods, food groups and dietary patterns, in order to ensure that nutritional requirements are met, to prevent all forms of malnutrition and NCDs, and to promote overall health (FAO, 2024). FBDGs already encourage the consumption of diverse foods and discourage the consumption of unhealthy foods. Some go further to encourage consumption of un- or minimally processed foods, but could be further leveraged to include more nuanced, contextually appropriate recommendations, informed by **microbiome research** (Armet *et al.*, 2022). Indeed, the incorporation of microbiome science with microbiome-focused endpoints into nutrition research may be a prerequisite to improve healthy eating (Armet *et al.*, 2022).

In an opinion paper, experts from MyNewGut, a multidisciplinary European project and consortium, suggest that in order to better support health, future dietary recommendations should consider not only human nutritional requirements, but also those of the gut microbiota (Sanz *et al.*, 2018).

The International Scientific Association for Probiotics and Prebiotics (ISAPP) has also proposed some steps to inform dietary recommendations for living microorganisms in fermented foods (Marco *et al.*, 2020, 2021, 2022). Given the importance of the first 1000 days in particular (as discussed in Section 3.1), such steps may hold further potential to improve health recommendations and develop educational programmes for optimal nutrition during pregnancy (including mode of delivery) and child feeding practices that support a healthy infant gut microbiome.

Encouraging higher consumption of dietary fibres, phytonutrients and more generally a diversity of plant foods and fermented foods has major implications for the agrifood system upstream. Given the strength of the evidence base, some policy intervention areas may be particularly relevant, and are outlined throughout the rest of this section. The possible implications of microbiome science with regard to food safety and food regulatory frameworks are also discussed.

Food processing

Food preparation and processing may be defined as "any change that is made to a food to alter its eating quality or shelf life", and is critical to make many foods edible, to enhance food safety and longevity, and to enhance appeal (FAO, 2004). Studies suggested that food processing and cooking techniques have an impact on the gut microbiome (Carmody *et al.*, 2019; Smith *et al.*, 2022) – much of which is negative in the case of highly processed foods. As such, many aspects of food processing and reformulation offer potential for adaptation, by taking into account their impact on the gut microbiome (Ercolini and Fogliano, 2018). For example, a major food company, Kuwaiti Danish Dairy, is reformulating some of its food products through "food re-engineering" that integrates gut health (Harlan *et al.*, 2023).

Some food processing techniques may alter the food matrix and involve the removal of protective structures such as bran layers, which are rich in fibres and polyphenols. Various debittering processes also reduce the amounts of polyphenols. Consuming minimally processed whole grains has better effects on glycemia than finely milled whole grains (Åberg *et al.*, 2020). New food formulations – or reformulations with multiple prebiotics, other dietary fibres and phytonutrients – are being developed, and may offer interesting options for encouraging the intake of dietary fibres, and/or for potential beneficial effects on health (Armet *et al.*, 2022; Ranaivo *et al.*, 2022). At the same time, caution is advised, as the consumption of processed products that are highly enriched in one type of fibre could have no, limited or even adverse effects when compared to the consumption of un- or minimally processed foods that are naturally rich in dietary fibres (Angelino *et al.*, 2019; Singh *et al.*, 2018). More data are also needed on the effects of food additives (as frequently found in highly processed foods) on the microbiome and health.

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Fermented foods result from microbial fermentation of diverse raw substrates. Fermentation processes have traditionally been appreciated because they can improve shelf life and safety, enhance nutritional and functional properties, and remove noxious compounds. As already discussed, these foods have a positive influence on the gut microbiome. The unique properties of fermented foods include live microorganisms (when not pasteurized or filtrated), and microbial metabolites resulting from the fermentation process. When it occurs naturally, the fermentation process is due to microbes that are naturally present in the raw foods and the environment, and this is the case for most traditional fermented foods. Alternatively, such foods may be produced using industrial processes, where fermentation is well controlled and based on starter cultures. Several starter strains have probiotic properties themselves. As fermented foods become integrated into the industrialized food system, a better understanding of the components that confer health benefits will be required – along with appropriate quality control and certification procedures – to ensure consumers can be informed of the health value of the wide array of products in this rapidly expanding market.

Food distribution

Several post-harvest treatments are being used to preserve the quality and safety of fresh food products. In this context, a better understanding of the microbiome of fresh food products (i.e. the microbial population naturally present in such products) may help to make important predictions on shelf life (Palumbo *et al.*, 2022). This may allow for better characterization of the spoilage process, while at the same time helping to identify specific bioprotection agents (e.g. microbial agents or networks that decrease spoilage). These are biocontrol-based products (typically yeast and bacteria) that are currently marketed for post-harvest applications. Interestingly, food storage and production could also modify the microbiome naturally present in plant tissues, which could eventually contribute to gut microbiome diversity if foods are consumed raw (Wassermann *et al.*, 2019; Wicaksono *et al.*, 2023a, 2023b).

Food production

In most countries, the consumption of a wide range of un- or minimally processed plant foods is not possible for many segments of the population – in part due to supply and/ or affordability constraints. Several measures should be taken to address these constraints, including policies aimed at:

- **Increasing agrobiodiversity:** Efforts are needed to increase the availability and diversity of cultivated crops. This includes underutilized and neglected traditional crops, and in particular species and varieties that are high in fibres and phytonutrients.

- **Plant breeding:** Many bioactive compounds – such as phytonutrients – have a bitter or astringent taste that does not appeal to consumers. As a result, these compounds are routinely removed from plant foods, through techniques such as selective breeding and processing. For example, the reduction of the bitter taste in Brassicaceae reduces glucosinolate, though it is a bioactive molecule which, when mediated by the gut microbiome, has a positive impact on human

health (Liou *et al.*, 2020). Similarly, certain "waxy" variants of cereal grains – such as rice, maize, sorghum, millet and wheat – that are low in resistant starch are widely used for their unique organoleptic characteristics (e.g. sticky rice), as well as for other physicochemical properties that are desirable for food processing. However, low levels of resistant starch have been shown to reduce microbiome diversity and SCFA production. Weight gain was higher in mice that were fed cereals with less resistant starch, than in mice who were fed the same portions of non-waxy cereal variants (Yang *et al.*, 2023). Conversely, plant breeding may also be used for the phytonutritional improvement of crops. A specific maize line (known as "quality protein popcorn"), producing seed proteins with substantially higher levels of the essential amino acids lysine and tryptophan, has been shown to have positive impact on the gut microbiome (Korth *et al.*, 2022). High throughput platforms have been developed to identify plant selective traits that could support healthy microbiome composition and/or functions (Yang *et al.*, 2022). Interestingly, the presence of some nutritionally interesting molecules such as prebiotic fructans may also increase plant tolerance to abiotic stress (i.e. freezing and/or drought conditions) (Livingston, Hincha and Heyer, 2009). Overall, policies are needed to promote crop breeding that is focused on improving phytonutritional content, while also maintaining phytonutrients that are beneficial to the gut microbiome.

- **Agricultural practices:** Several biotic and abiotic factors – such as crop management, harvest season, soil quality, available nutrients, light and water – impact fibre and phytonutrient content. Seasonality may also be important. Inulin, for example, protects plants from freezing, and its content may increase under cold conditions (Özcan *et al.*, 2019; Winardiantika *et al.*, 2016). Agricultural practices will also impact the presence of potential residues of pesticides, veterinary drugs and other exogenous compounds.

Waste valorization

Agro-industrial waste such as wood and fruit peels are rich in carbohydrates, and could be used to produce prebiotic polymers for human consumption (Han *et al.*, 2022; La Rosa *et al.*, 2019; Vazquez-Olivo, Gutiérrez-Grijalva and Heredia, 2019; Wongkaew *et al.*, 2021). Policies that specialize in a circular economy – including start-up grants for small-scale enterprises (both urban and rural) – can serve as an important incentive to valorize wood and food processing waste.

Food regulatory framework

Risk assessment: Research on microbiome interactions with exogenous chemicals may provide additional insights into human health risks resulting from chemical exposure. Chemical risk assessments are conducted to evaluate the safety of food additives, chemical residues in food, environmental pollutants and contaminants – and to provide the basis for establishing health-based guidance values. Given their impact on the agrifood system however, regulatory decisions must be carefully weighed. Currently, there are many discussions regarding the potential integration of considerations related to the microbiome in chemical risk assessment (FAO, 2023b, 2023c, 2023d; Merten *et al.*, 2020; Piñeiro and Cerniglia, 2021). But although

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microbiome potential is widely recognized, the applicability of microbiome-related data to chemical risk assessment is still limited. Multidisciplinary collaborations between risk assessors, microbiome scientists and regulators are therefore needed in order to (i) identify gaps and needs, (ii) develop approaches for evaluating and integrating microbiome-related data, and (iii) define or update existing assessment frameworks (FAO, 2023b, 2023c, 2023d).

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Concluding remarks

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One of the most important findings from microbiome science so far, is that **the first 1000 days of life are critical for the development of the human gut microbiome, with important health impacts throughout life – including on undernutrition, obesity and NCDs.** Maternal nutrition, mode of childbirth, breastfeeding, weaning practices, other infant and young child feeding practices, and exposure to antibiotics are all key factors that impact the development of a healthy gut microbiome during this specific time period. The gut microbiome plays a critical role in child malnutrition, and its treatment and may be targeted via therapeutic feeding. This finding not only emphasizes further the importance of this period for nutrition, health and development, but may also provide further insights into pathways for addressing malnutrition.

Beyond the first 1000 days of life, **lifelong adherence to a healthy diet is crucial for health, growth, development and the prevention of all forms of malnutrition. Microbiome science may provide additional insights and evidence to further refine recommendations**. FBDGs already provide contextually appropriate recommendations for high consumption of diverse un- and minimally processed plant foods. New evidence emerging from microbiome science may provide the basis to further refine such guidelines, to include even higher intake of dietary fibre and the consumption of a range of fermented foods, among others. Apart from dietary approaches, specific foods (such as MDFs), and products (such as biotics) may also play a role, especially when targeting more specific health problems.

This paper indicates that **for the potential of microbiome science to be realized, there is first and foremost a need for further research. This should be carried out using standardized protocols, as well as interdisciplinary and citizen-science approaches**, to determine how factors in the diet (as well as upstream in the agrifood system) affect the role of the human gut microbiome on nutrition and health.

Much of the current research is conducted in HICs. A stronger focus is needed on LMICs, in particular to account for their specific contexts and developments in their agrifood systems, dietary patterns, nutrition and health outcomes. To this end, scientists and stakeholders from these countries must be involved in microbiome science and innovation efforts.

The paper highlights **various entry points for changing both consumption patterns and agrifood systems, in order to exploit – soon – the role of the microbiome in the prevention and treatment of all forms of malnutrition and diet-related NCDs**. These entry points include FBDGs, nutrition and health education and consumer awareness programmes, the management and regulation of the food environment, food product development and processing, crop diversification and breeding, and various nutrition programmes – including supplementary feeding, food fortification, therapeutic feeding, school feeding and local procurement, among others.

Microbiome science continues to demonstrate how our human microbiome and health may be more closely connected than previously thought, to the microbiome and "health" of our environment, and that both are potentially linked by our agrifood systems. In addition, sufficiently robust microbiome science – along with a better understanding of food–microbiome–host interactions – may enable the integration of microbiome data in processes supporting food safety.

These findings urge us to adopt more integrative and holistic approaches, based on coordinated multidisciplinary, multisectoral and interagency cooperation. In this regard, FAO has a comparative advantage, as unpacking complex agrifood system issues, engaging with multiple stakeholders, and bridging boundaries between science and policy are among its core functions.

Microbiome science and innovation have the potential to help us accelerate progress and strengthen impact across many of the Sustainable Development Goals (SDGs), in particular SDG 2 (Zero Hunger), SDG 3 (Good Health and Well-being), SDG 9 (Industry, Innovation and Infrastructure) and SDG 12 (Responsible Consumption and Production).

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ISBN 978-92-5-139001-6

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CD1778EN/1/07.24