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1.1 Introduction

The microbiota refers to the total population of microbes that co-exist with the host, whereas the microbiome is the regulated genomic composition of the microbiota. The microbiome was initially coined to study the co-existing relationship between microbes and the hosting environment by Mohr in 1952 but only gained attention and recognition in the genomic era during the early 2000s [1, 2]. Microorganisms are present everywhere in our daily lives, establishing transient or permanent interactions with the human host. It is estimated that around 10–100 trillion microbes are present in the human body [3]. Although many different types of microbes co-exist in human bodies such as viruses, fungi, and protozoa, bacteria are the most well studied and represented for their largest proportion and intimate relation with human health. The microbiota is shaped by the host's biochemistry, nutrition intake, and lifestyle pattern. In kind the microbiome influences human health through nutritional processes, immunomodulatory functions, manipulating the host behavior, and influencing disease pathogenesis.

Thus, in this chapter, we will discuss how diet affects the host microbiome. The chapter will be divided into four parts. First, a general introduction to the basis of the host-microbiome and how various microbiomes interact with each other. Second, the varied diet-microbiome influence on different income, age, and location factors. The third subchapter 1.3 will look into the application of diet in shaping the microbiome to treat various diseases. Lastly, the global outlook of opportunities and challenges in microbiome data study to achieve global health.

1.1.1 Microbiome Diversity in Human Body

Regional microbiota varies at different parts of the human body or organs resulting from the changes of the environment that is established by the host

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biochemistry and the pre-existing microbes that inhabit the area. Thus, it is safe to say that no two persons' microbiome is identical since the equilibrium of the microbiome is constantly altered in individual hosts over the various stages of growth as revealed by multiple research studies [3]. Strikingly in 2007, an international effort to characterize the microbial communities in the human body called the Human Microbiome Project (HMP) set forth to establish a "healthy cohort" reference database using hospital-acquired samples [4, 5]. The HMP, a US National Institutes of Health (NIH) initiative capitalized on the decreasing cost of whole-genome sequencing technology and advanced metagenomic sequencing technology to systematically map out these microbiome variations in healthy and diseased patients [4-6]. The first phase of HMP studied samples isolated from five major body sites: nasal passages, oral cavities, skin, gastrointestinal (GI) tract, and urogenital tract [4, 6]. As this book chapter is on the subject of diet-related influences on the microbiome, we will discuss more on the oral and gastrointestinal microbiome and briefly touch on the microbiome of other sites.

1.1.1.1 Oral Microbiome

The oral microbiome consists of diverse microbial populations that are categorized into individual niches based on localization preferences. These microbial niches vary regionally from the hard surfaces (teeth, dental prosthetics, and dental appliances) to mucosal surfaces (oral palate, cheek tissues, gingiva, tongue, and palatine tonsils). This variation is due to the accessibility of the microbes to nutrients and specific microenvironment changes generated by the brief passage time of food in the mouth. Currently, Human Oral Microbiome Database (HOMD) includes over 700 species of bacteria, where 57% are named, 43% are unnamed (13% are cultivated and 30% are uncultivated phylotypes) [7]. Through 16S rRNA gene sequencing, the HOMD established over 1000 taxa, where approximately 600 taxa are named and distributed in 13 different phyla, including Actinobacteria, Bacteroidetes, Chlamydiae, Chloroflexi, Euryarchaeota, Firmicutes, Fusobacteria, Proteobacteria, Spirochaetes, SR1, Synergistetes, Tenericutes, and TM1 [7] (Figure 1.1). These collective populations of microbes exert important host dietary functions involved in the metabolic, physiological, and immunological aspects. These include oral cavity health and also the perception of taste and smell [13].

The oral microbiota plays an important role during the initial development phase (3–14 months of age) and the transitional phase (15–30 months of age) in human infancy. This is due to the under-developed gastric function that in turn results in the presence of microbes found in the daily encounter to be present in the stool samples of infants from the age of 3–30 months. Two continuous studies were conducted to link the role of gut microbiome progression and young age diabetes under the program called The Environmental Determinants of Diabetes in the Young (TEDDY) [14, 15]. In these studies, it was found that microbes found influenced by geographical factors, such as exposure to siblings, household pets, and day-care exposures, were found in the infant's microbiome. Additionally, microbes isolates found in breast milk and baby food were found to be present in the infant fecal excretions [14, 15]. Furthermore, parents and guardians chew



Figure 1.1 The average adult human microbiota composition of five body sites and their dominant phyla. Oral microbiome mainly comprise *Firmicutes* (36%), *Actinomycetes* (25%), and *Proteobacteria* (22%) [8]; respiratory system microbiome mainly comprise *Firmicutes* (39.4%) and *Bacteroidetes* (23.5%) [9]; gut microbiome is dominated by *Firmicutes* (53.9%) and *Bacteroidetes* (35.4%) [10]; skin microbiome is dominated by Actinomycetes (51.8%) [11]; and urogenital tract microbiome is dominated by *Firmicutes* (61.9%) [12]. Source: Based on Zaura et al. [8], Moffatt et al. [9], Goodrich et al. [10], Grice et al. [11], and Hilt et al. [12].

soft food prior to feeding the chewed foods to infants in certain cultures, effectively transferring the oral microbiome from the parents/guardians to the infant [16]. While the terminology diet often refers to the role of food and beverages proffered to the individual, it further includes the microbes that are in contact with the oral region, such as aerosol dense microbes and microbes existing on the surfaces of daily-used items.

Thus, it is evident that the human oral microbiome plays an important role in shaping the initial gut microbiome, laying the foundation of the general microbiota composition upon entering the stable phase after the individual reaches over three years of age.

1.1.1.2 Gastrointestinal Microbiome

Comparing the various human microbiomes, the gut microbiota constitutes the majority of the microbes in the human body, while presenting the most complex diversity and dynamics between individual members of the microbiota community. The microbiota niches span across the gastrointestinal (GI) tract, where each region (stomach, duodenum, jejunum, ileum, large intestine, and rectal regions) has large environmental variations (pH, soluble oxygen, nutrient, bile salts, and so forth) that promotes the diversity resulting in selective pressure to shape the microbiome. The gut microbiome development can be traced to pre-natal gestation, where the microbes found in the placenta show similar

profiling to the maternal microbiome [17]. Post-delivery, the gut microbiome is initially shaped by the microbes that are introduced via the oral cavity for the first three years of age. After the individuals, the digestive system is fully developed, the microbiome shifts into the stable phase [14, 15]. Despite extensive efforts to map the gastrointestinal microbiota, the process of classifying the intestinal microbiome is far from complete.

Gastric microbiota is generally known to be acid-tolerant, where these microbes need to survive under low pH conditions (pH 1–5). In a healthy individual, metagenomic analysis of the gastric microbiota showed an average abundance of *Firmicutes* (29.6%), *Bacteroidetes* (46.8%), *Actinobacteria* (11%), and *Proteobacteria* (10%). Among these phyla, the predominant genus includes those from the acid-tolerant *Streptococci, Lactobacilli, Staphylococci,* and *Neisseria* spp. [18, 19] Dysbiosis resulting from *Helicobacter pylori* infection showed a massive shift of *Proteobacteria* abundance accounting for 93–97% of the total microbiota count [19]. The pathogen *H. pylori* preferentially localize at the upper gastric mucosa perturbing the gastric microbiota by reducing the microbial diversity and is linked to medical problems such as gastritis, peptic ulcers, and cancer [20].

The small intestine involved in nutrient absorption with a long, narrow, folded tube structure exhibits restricted nutrient accessibility to promote microbial growth. The primary composition of the small intestinal microbiota is from the *Clostridium, Enterococcus, Oxalobacter, Streptococcus,* and *Veillonella* genera. Despite the poor diversity, the microbiota composition fluctuates depending on the structure and the exposure to the digested chyme in the small intestine [21]. Most of the microbes colonizing the small intestine carry genes encoding for carbohydrate phosphotransferase that play a role in competitive carbohydrate uptake in the microbiome [22]. Dysbiosis in the small intestinal tract showing increased abundance of *Bacteroides* spp., *Clostridium leptum,* and *Staphylococcus* spp. is linked to pediatric celiac disease [23], while the increased abundance of *Escherichia coli* and *Roseburia* spp. is often observed in patients with ileal Crohn's disease [24].

The large intestine (including the cecum, colon, and rectum) has the highest microbiota density in the whole body with approximately 10¹² cells per gram, weighing about 1.5 kg in an average adult. The colorectal microbiota is dominated by phyla *Firmicutes* and *Bacteroidetes* that account for more than 80% of the total microbial population in adults [25, 26]. Studies have shown that certain predominant species in the gut populate the colorectal region based on the presence of dietary nutrients. *Bacteroides* were found to be enriched in a carbohydrate-rich diet, while dietary mucin and complex sugars encourage the abundance of *Prevotella* and *Ruminococcus*, respectively [27].

1.1.1.3 Skin Microbiome

Similar to the oral microbiome, skin microbiota varies at different locations depending on the presence of hair, sebum secretion, moisture, host biochemistry, and exposure to air [28]. The primary colonizers of the skin surfaces are predominantly *Staphylococcus epidermidis*, other coagulase-negative *Staphylococci*, and *Actinobacteria* (from the genera *Corynebacterium*, *Propionibacterium*, *Brevibacterium*, and *Micrococcus*) [28] (Figure 1.1). The skin microbiota confers direct health benefits by occupying a wide range of skin, generating a shielding effect from the environmental pathogenic [28]. Through indirect interaction, certain skin commensal microbes can thrive in the subepidermal layer [29], establishing a link between the skin microbiome and the host immune system. Additionally, skin microbiota is known to affect the food quality particularly in fermented foods, where the by-products of the fermentation, in turn, affect the host gut microbiota [30].

1.1.1.4 Respiratory Microbiome

The current studies of the human respiratory microbiome focus on the lung microbiota, particularly in the bronchial microbiome. Samples of the human lungs are acquired using a deep nasal swab (for nasopharyngeal sampling) [31] and sputum collection (for bronchoalveolar sampling) [32]. In the lungs of a healthy person, the typical microbiota includes those from the genera of *Firmicutes, Bacteroidetes, Proteobacteria, Fusobacteria,* and *Actinobacteria* [33, 34] (Figure 1.1). These microbes thrive at mucosal surfaces of both the lung and bronchus where the exchange of oxygen and carbon dioxide happens; therefore, most of these microbes are facultative anaerobes able to survive in the varying levels of oxygen [9]. While the study of the respiratory microbiome requires further in-depth understanding, these microbes certainly play an important role in various respiratory diseases such as bacterial pneumonia, cystic fibrosis, asthma, and chronic obstructive pulmonary disease (COPD) [31].

1.1.1.5 Urogenital Microbiome

The urogenital microbiome interacts with various aerobic and anaerobic microorganisms with the host, including microbes from the bladder [35, 36] and reproductive tract [37]. The microbiota bladder and urinary tract include aerobic bacteria such as E. coli and Enterococcus faecalis [38], and anaerobic bacteria such as Corynebacterium, Lactobacillus, and Ureaplasma [39–41]. The vaginal microbiota comprises mainly Lactobacillus spp. and Bifidobacterium [42] that prevent pathogenic infections by acidifying the lower genital tract. Patients suffering from interstitial cystitis showed lower bacterial diversity with enriched populations of Lactobacillus (92% of the total microbial population) compared to the abundance in healthy individuals (57% of the total microbial population) [35]. The changes in urogenital microbiota were found to be linked to other medical ailments and chronic inflammatory diseases such as inflammatory bowel disease (IBD) [43], suggesting a link between the urogenital microbiome and the digestive tract. Therefore, the study of the urogenital microbiome can be used as a good indicator to determine the host health by using patient urine samples.

1.1.2 Elements that Influence Microbiome Development

Various elements play a role in shaping the respective microbiome in the human body. Extensive studies comparing the variation of the gut and skin microbiome of twins suggest that the genetic component does play some role

in modulating the microbiome, it is the daily habits, interactions, and age that has a stronger influence on the development of the microbiome [44, 45]. A longitudinal study conducted to investigate the oral microbiome variation between monozygotic and dizygotic twins showed that diet plays an important role to shape the microbiome. This study looks at the demineralization of enamel and salivatory composition that showed that food preferences and eating habits (including eating etiquette) help shape the microbial community. These include the formation of multispecies biofilm communities that establishes a stronger foothold in the microbiome. It was shown that there are great variations between the microbiome of twins, although there is a closer similarity of microbiome between monozygotic twins in comparison to dizygotic ones [44]. In another study comparing the core gut microbiome of obese and lean twins similarly showed variation between the microbiome of twins, where monozygotic twins have closer similarity to each other, while dizygotic twins were shown to resemble the maternal microbiome. This observation is similar for both obese and lean twins observed in this study [45]. Thus, it is certain that the dietary role plays an important factor in the establishment and maintenance of the host microbiome. This will be discussed at length in the subchapter 1.2, addressing the nutrition-based role in changing the microbiome landscape. However, before we delve into subchapter 1.2, we here address basic terminologies used in the following part of this chapter.

1.1.2.1 Prebiotics

Prebiotics comprise mainly specialized plant fibers that play a role in enhancing the proliferation of selected groups of microbes. These fibers can exist as both soluble and non-soluble fibers, where they function to retain and stabilize certain microbial populations. The role of prebiotics is most prominent in the GI tract, where the addition of prebiotics enhances glucose metabolism and reduces the risk of developing metabolic diseases such as diabetes and obesity [46, 47].

1.1.2.2 Probiotics

Probiotics are live beneficial microbes that supplement certain health-benefiting functions lacking in the human host [48, 49]. To qualify as a probiotic, the microbes must be resistant to gastric juices and bile acids, compete with the local microbiota, and localize in the gut for a short period, on top of having health-benefiting properties [50]. There have been extensive studies suggesting that probiotics confer health-benefiting properties [51] and alleviate negative side effects of antibiotic-associated diarrhea [52]. There are various probiotics from different phyla, such as *Lactobacillus* sp. and *Bacillus coagulans (Firmicutes), Bifidobacterium (Actinobacteria), E. coli* Nissle 1917 (*Proteobacteria)*, and *Saccharomyces boulardii* (Ascomycota). It is well documented that certain probiotics such as *E. coli* Nissle 1917, *S. boulardii*, and certain *Lactobacilli* have been used to treat gastrointestinal infections and gut-related complications [48]. Spore-forming bacilli such as *B. coagulans* were used to treat rheumatoid arthritis through gut-mediated anti-inflammatory properties [50]. Other studies have also shown that *S. boulardii* have been used to treat skin wound infections,

while *Lactobacilli* are commonly used to maintain healthy vaginal flora to prevent bacterial vaginosis (BV).

1.1.2.3 Diet and Nutrition

The dietary habits and nutritional composition influence the microbiome, thus affecting the host health. The food distribution based on living standards, the supply of local foods, and cultural habits influence people's dietary habits from different walks of life. In the consumption of these food groups, the nutritional content alters the preference of microbial growth in the GI tract. This diversity is time-dependent, where the microbiome profile is highly dynamic providing daily cyclical fluctuations that are influenced by the eating habits and daily routine [53]. For instance, individuals consuming a meat-rich diet showed an increased diversity of bile-tolerant microorganisms (*Alistipes, Bilophila*, and *Bacteroides*). They decreased polysaccharide hydrolyzing-*Firmicutes* compared to the vegetarian diet [54]. Comparatively, intermittent fasting in mice showed cyclical changes in the gut microbiome, affecting all major phyla where *Firmicutes* peaks during nocturnal feeding, whereas *Bacteroidetes* and *Verrucomicrobia* species peaked during daytime feeding [53].

These dietary patterns indicate the roles of diet affecting the gut microbiome, where this topic would be further discussed in the following subchapter 1.2.

1.1.3 Current Approaches Employed in Studying the Human Microbiome

As mentioned in the introduction, the era of multi-omics studies propelled microbiome research with the advancement in 16S ribosomal RNA sequencing and shotgun metagenomic sequencing technologies. This gave rise to big data analysis of bioinformatics data acquired from donors of various backgrounds and health states, providing various new platforms to accelerate the analysis of large datasets, such as gcMeta [55] and MicrobiomeAnalyst [56].

Employing 16S rRNA gene sequencing enables the profiling of most prokaryotic amplicons that accurately classify and identify prokaryotes on a routine basis [57, 58], providing a reliable evidence to support phylogenetic study [59]. On the other hand, shotgun metagenomic sequencing provides a closer understanding of the total genomic DNA makeup of an isolated microbe. This approach provides the complete profiling of the isolated microbe to investigate the unique traits of the microbes and its role in the microbiome (e.g. metagenomic assembly and binning, metabolic function profiling, and antibiotic resistance gene profiling) [60, 61].

These technologies provide researchers with a glimpse of the gut microbiome composition, facilitating research breakthroughs on the role of each individual microbial group and their roles in a state of equilibrium. The prospect is optimistic, but further refinement of the technique is needed to understand the many unclassified components of the microbiome that has yet to be annotated.

1.2 Dietary Lifestyle Variation Affecting Host Microbiome

In section 1, we have introduced that dietary nutritional content impacts human gut microbiota including up to 10¹⁴ anaerobic microorganisms from over 1,000 different species [62]. While it is certain that diet plays an important role in shaping the microbiome, however, the differing lifestyle is a major determining factor in influencing the dietary pattern. This section will first look at the role of nutrition influencing the gut microbiome, followed by a closer inspection on the dietary differences of individuals of different wealth, ages and locality.

1.2.1 Dietary Role in Shaping the Microbiome

Dietary habits and nutritional composition are a few of the most important and modifiable determinants of human health. Habitual diet is postulated as an essential determinative factor to establish the initial human gut microbiome. Among them, carbohydrates, fat, protein, vitamin, water, and inorganic salt are the six major nutrients needed by the human body. While it is certain that each of these major nutrients plays an important role in shaping the microbiome, other factors synergistically exert their influence such as gender, body mass index (BMI), cultural, economic, social socioeconomic status, and lifestyle (e.g. smoking, alcohol drinking, and physical activity) [63]. The intake of these dietary nutrients facilitates various cellular functions such as tissue repair, homeostatic biochemical equilibrium, and host development. These cellular activities are not just limited to the host cellular response to the nutrient abundance but are also dependent on the microbiota response to these nutrients, altering the population and behavior of individual microbial groups. Herein, we discuss the role of protein, soluble saccharides, fibrous insoluble polysaccharides, and lipids in shaping the microbiome.

1.2.1.1 Protein and Polypeptides

The high nitrogenous content of dietary protein and peptides provides amino acids essential to both the host biochemistry and its microbiota. Most organisms require the essential 20 different amino acids to facilitate their cellular function [64]. The human host–microbiome favors the retention of certain microbiota population that helps break down protein complexes, providing the host with better absorption of these digested protein products. Some of these microbes thrive in the small intestine, such as *Klebsiella* spp., *E. coli, Streptococcus* spp., *Succinivibrio dextrinosolvens, Mitsuokella* spp., and *Anaerovibrio lipolytica*, which secretes various proteases and peptidases to facilitate protein digestion in the human gut [65].

High-dietary protein can change the microbiota composition by favoring microbes that can metabolize exogenous proteins. Certain microbes from the genus *Bacteroides* and *Lactobacillus johnsonii* naturally secrete proteases to digest dietary proteins and facilitate microbial localization in the small intestine [66]. These microbes establish a form of commensalism with the host, where

	Microbial diversity	Bifido- bacteria	Lacto- bacilli	Bacter- oides	Alist- ipes	Bilo- phila	Clost- ridia	Rose- buria	Eubacterium Rectale	References
Animal protein	ſ	↑↓		↑↓	¢	ſ	ſ	Ļ	↑↓	[54, 69, 70]
Whey protein extract	Ť	Ť	Ť				Ļ			[71, 72]
Pea protein extract	Ŷ	¢	Ť							[73]

Table 1.1 Effects of dietary protein on host-gut microbiota.

Source: Singh et al. [68]/Springer Nature/CC BY 4.0.

the digested amino acids are utilized both by the microbe and human host via absorption through the intestinal epithelial tissue. Microbiome dysbiosis caused by protein deficiency, such as a vegetarian diet, results in the depletion of protein-metabolizing populations and triggering intestinal inflammation [67].

Beef-based protein-rich diet showed the lower abundance of *Bifidobacterium adolescentis* and enriched *Bacteroides* and *Clostridia* abundance, indicating that meat-derived protein source can influence the development of the host microbiome [68]. The correlation of gut microbes to protein diet is summarized in Table 1.1.

1.2.1.2 Soluble Saccharides

Soluble saccharides can be divided into simple saccharides (glucose, fructose) and complex polysaccharides (starch), where these sugars provide the energy to the cells. Overconsumption of these sugars is often attributed to various health problems such as obesity, diabetes, cardiovascular disease, liver disease, and tooth decay [74-76]. The presence of high dietary simple sugar content (glucose and fructose) influences the primary metabolism in gut microbial by upregulating sugar transport proteins to increase cellular uptake of the sugar. Similarly, secondary metabolic pathways expressing polysaccharide utilization genes are suppressed in the presence of simple sugars [77]. This phenomenon is commonly observed in Bacteroides thetaiotaomicron that maintain the microbes in their planktonic lifestyle and inhibiting microbial colonization [78]. The suppressed genes include those involved in bacteria biofilms [79] and upregulate genes involved in chemotaxis [80]. The chemotaxis genes include flagella formation that can stimulate the host immune system through interaction with TLR5, as seen on the pathogenesis of the opportunistic pathogen Burkholderia cenocepacia infecting the host [81]. The effects of soluble sugar in the human gut microbiota is summarized in Table 1.2.

1.2.1.3 Dietary Fibers

Dietary fibers are non-soluble polysaccharides that form the structural component of the plant. These fibers function as prebiotic source, where they form

	Bifidobacteria	Bacteroides	Clostridia	Lactobacilli	References
Glucose	1	Ļ			[82, 83]
Fructose	1	\downarrow			[82, 83]
Sucrose	1	\downarrow			[82, 83]
Lactose	1	t	\downarrow	1	[84]
Artificial sweeteners	\downarrow	1	Ļ	Ļ	[85]

 Table 1.2 Effects of natural and artificial sugar on gut microbiota.

Source: Based on Hanuszkiewicz et al. [81].

scaffolds for microbial localization and further serve as substrates for microbial fermentation. These fibers include fructans, polydextrose, fructooligosaccharides (FOS), galactooligosaccharides (GOS), xylooligosaccharides (XOS), and arabinooligosaccharides (AOS) [86]. Fiber-rich diets, such as those of vegetarians and vegans, were found to help alleviate health problems including cardiovascular diseases and cancer [87]. Fiber-rich diet showed a depletion of *Bacteroidetes*, *Clostridium* and *Enterococci* abundance, and trigger the increase of lactic acid bacteria, Ruminococcus, Eubacterium rectale, and Roseburia abundance. In the presence of dietary fibers, these lactic acid-producing bacteria ferment the fibers to produce short-chained fatty acids (SCFA) such as acetate, propionate, and butyrate [88]. These SCFA influence the growth of some microbes in the gut, exerting health-benefiting properties including regulating pathogenic microbial growth [89]. A higher percentage of Bacteroides was found in the intestines of people eating Western diets, while those who ate fruits and beans from a high-fiber diet found the opposite [90]. The summary of how dietary fiber affects the gut microbiota is shown in Table 1.3.

1.2.1.4 Lipids

Fat-rich diets including saturated fats from animal foods negatively affect the gut microbiota, leading to poor metabolization of the nutrient and ultimately leading to obesity. Studies involving murine models showed depletion of *Bacteroidetes* and *Bacillus bifidus* abundance and enrichment of *Firmicutes* and *Mollicutes* in mice fed with a high-fat diet [93]. However, such effects on the microbiome are less severe in mice fed with moderate amounts of polyunsaturated fats such as

	Bacterial abundance	Gene	Lacto- s bacilli	Bifido- bacteria	Clost- ridia	Enter-	Rose- s buria	Eubac- teria	Rumin- ococcus	Refer- ences
Fiber/ prebiotics	1	1	1	1	ţ	¢↓				[70, 91]
Resistant starch	1	1	1	1			1	1	1	[70, 91, 92]

 Table 1.3 Effect of non-digestible carbohydrates on gut microbiota.

Arrow thickness corresponds to the relative number of studies supporting the relationship. Source: Based on Glick-Bauer and Yeh [90].

	Lactic acid bacteria	Bifido- bacteria	Clostr- idiales	Bacter- oides	Bilo- phila	Faecali- bacterium prausnitzii	Akkermansia- muciniphila	References
High fat	ţ	Ť	1	1				[70, 95, 97, 98]
High saturated fat		I		1	1	Ť		[95, 96]
High unsaturated fat	1	1					1	[95, 99]

Table 1.4 Effect of dietary fat on gut microbiota.

Lactic acid bacteria include *Lactobacillus* and *Streptococcus*. Source: Based on Walker et al. [92].

omega-3, omega-6, and omega-9 [94]. Similarly in human studies, a high-fat diet increases the abundance of anaerobic microbes and *Bacteroides* [95, 96]. Patients adapting a low-fat diet showed the increased fecal abundance of *Bifidobacterium* and decreased proportion of *Faecalibacterium prausnitzii* [95]. Table 1.4 summarizes the effect of dietary fat on the gut microbiota.

1.2.2 The Socioeconomic Impact on Diet-Related Microbiome Changes

Access to proper living conditions, sufficient nutrition, and clean water severely affect the host microbiota [100]. Maslow's hierarchy of needs can be generally divided into three main needs categories: basic, psychological needs, and self-fulfillment (Figure 1.2a) [102]. Poorer nations with lower gross domestic product (GDP) per capita have limited access to different types of foods, comprising mostly simple carbohydrates. They are also granted limited access to clean water, resulting in poor sanitary conditions. This can be seen in a number of nations in the African continent and some Southern American countries (Figure 1.2b-e). People within these wealth groups require basic needs and are usually underfed, where some might be under-nourished. Citizens from countries within the middle-income range have access to foods that can meet the dietary requirements. These people have psychological needs, where despite having the same dietary access as countries with high GDP, these people can satisfy their needs adequately due to their limited spending power [103]. Citizens of the developed countries with high GDP are generally regarded as having self-fulfillment needs. Due to a surplus of foods and greater spending power, citizens in these countries adopt dietary habits based on their personal preferences. This results in higher consumption of meat, dairy products, sugary products, and processed foods resulting in increased incidences of diabetes and obesity [104]. Countries falling under these categories are nations from Northern America, Western Europe, and East Asian (Figure 1.2b-e).

On top of access to different diets, individuals of wealthier groups also have access to certain types of dietary luxuries due to their purchasing power. Such



Figure 1.2 The socioeconomic impact on dietary habits. (a) The schematic of Maslow's hierarchy of needs and the different categories of needs. (b) The global distribution of average income generated per annum wealth [101]. (c) The global percentage of obese patients in different nations. (d) The global average consumption of sugar per individual. (e) The global average consumption of meat per individual. Source: Based on LaMagna [101].

dietary luxuries include access to alcohol, tobacco, and fatty foods (e.g. foie gras, caviar). The consumption of alcohol and tobacco has been known to perturb the gut microbiota populations [105]. The exposure of compounds found in drinking and chewing tobacco can influence the mucosal layer in the GI tract that serves as the initial protective barrier against pathogenic microbial colonization [106]. Chewing or smoking tobacco was found to increase the abundance of anaerobic bacterial species in the oral cavity and upper GI tract, where there was observable perturbation in the oral microbiota from the genera of *Actinobacillus, Porphyromonas, Lautropia,* and *Bifidobacterium* [107, 108]. Similarly, the chronic exposure of alcohol to the oral and GI microbiome reduces the abundance of *Akkermansia muciniphila* (*Verrucomicrobia* phyla) that exhibits anti-inflammatory properties [109]. Thus, based on the wealth of the individual, the dietary habits influence the gut microbiome and the host health as a whole.

1.2.3 Age Groups and Dietary-Related Microbiome Changes

The composition of the average human's microbiome changes over the span of their lifetime, where these changes are attributed to the individual's basal metabolic rate (BMR), host biochemistry, lifestyle, and dietary habits. The BMR of an average individual peaks around the late teenage years and declines as the individual ages. Coupled to the eating habits, the gut microbiota changes depending on these factors, where the composition of the gut microbiota shows vast differences at different growth stages (Figure 1.3).

The initial development of the human gut microbiota is shaped during birth through microbial colonization introduced by the environment. During gestation, fetuses are generally considered germ-free *in utero*, where the



Source: A. (Schwartz et al., 2012) B. (Koenig et al., 2011) C. (Monira et al., 2011) D. (Biagi et al., 2010) E. (Zhang et al., 2009)

Figure 1.3 The composition of the gut microbiome in people at different age stages. Source: Based on Koenig [110] and Biagi et al. [111].

gut microbes of the individual microbiota are introduced post-delivery. The microbiome is shaped by initial microbes introduced during childbirth, where infants delivered through natural birth and Caesarean-section (C-section) have different microbiota composition [18, 112, 113]. The GI tract of infants delivered by natural birth is primarily colonized by maternal vaginal and fecal bacteria with the enriched abundance of Lactobacillus and Bifidobacterium spp. [114], whereas the GI tract of C-section infants is colonized by other environmental bacteria [112]. The microbiome is further shaped by the infants' diet, where the breast-fed infants have more heterogeneous microbiota with higher taxonomic diversity than formula-fed babies [115]. These variations in the delivery method and diet contribute to the maturation of the infant's immune system through the gut microbiome development [116]. Breast-fed infants have further exposed microbes present in the milk and breast surface, accounting for over 700 species of bacteria [117] made up primarily of Streptococci and Staphylococci [118]. Breast milk is also rich in complex oligosaccharides that stimulates the growth of beneficial microbial groups such as Staphylococci [118] and Bifidobacteria [119]. In comparison, the microbiota of formula-fed babies adapts a microbiota similar to that of an adult, with an increased abundance of E. coli, Clostridium difficile, Bacteroides fragilis, and Lactobacilli [120, 121]. The microbiota during the age of 0-3 years old is highly dynamic, which stabilizes after the age of 3 years [122].

Children (3-10 years old) undergo massive changes in the microbiota composition, particularly due to the introduction of solid dietary foods. Food solids comprise various nutrients and fibers that facilitate the colonization of various microbial groups including butyrate producers such as *Bacteroides* and certain *Clostridium* species [110, 123]. The diet introduced during the pre-adolescence phase influences how the microbiome takes shape, where children provided with a balanced diet (meat/fish, fruit, vegetables, eggs/beans, and bread/pasta) showed different microbiota shift compared to those given an unhealthy diet (processed, sugar-rich, and fatty foods) [124]. A study conducted in Japan discovered that Ruminococcus and Bacteroides were found to be enriched in children provided with unprocessed foods (e.g. meat/fish, fruit), whereas Blautia and Clostridium were abundant in the GI tract of children provided with processed food. Additionally, micronutrients provided through nutritional beverages were found to influence the microbiota population. Children provided with the Growing Up Milk-Lite (GUMLi) was found to have increased bifidobacterial abundance compared to natural bovine milk and other milk formulations [124], indicating that micronutrients can be used to alter the microbiota.

The microbiota diversity in adults is similar to the children gut microbiome, but varies in the abundance of the various groups where adults showed a lesser abundance of *Actinobacteria*, *Bacilli*, *Bifidobacterium*, *Faecalibacterium* spp., *Clostridium* cluster IV (*Ruminococcaceae*), and *Bacteroidetes* [125, 126]. *Clostridium* cluster XIVa (i.e. *Butyrivibrio crossotus* and related bacteria), *Firmicutes*, and *Bacteroides* were more abundant in adults than children [127–129]. Other phyla showing a lower abundance in average adults include *Proteobacteria*, *Verrucomicrobiota*, *Actinobacteria*, and *Euryarchaeota*; where the various microbiota members play a role in microbes maintaining the host

immune homeostasis [130]. The adult microbiota is relatively stable but can be perturbed by changes in diet, physical activity, illness, and changes in hormonal cycles and medical therapies. Alternations of the microbiome may positively or negatively impact the host health, where the microbiome is linked to various medical issues [131]. This will be discussed in the following subchapter 1.3.

The composition of the intestinal microbiota of people in their golden age (>65 years) differs largely between individuals [132]. These microbiota differ even further compared to the diversity of core microbiota in younger adults [111, 132]. The gut microbiome of elderlies has increased abundance of facultative anaerobes (such as *Proteobacteria* and *Bacilli*) and decreased abundance of *F. prauznitzii* and *Clostridium* cluster XIVa bacteria. It was also reported that centenarian's microbiota shows decreased abundance of *Bacteroides, Bifidobacterium* and *Enterobacteriaceae*; and enriched *Clostridium* spp. abundance [133].

The composition of the microbiota is certainly influenced by age; however, the dietary habits during infancy and pre-adolescence play an important role in shaping the diversity of the microbiota. The dysbiosis of the microbiota during adulthood alters the host biochemistry, resulting in the changes of the host immune system, behavior, and susceptibility to disease.

1.2.4 Continental Dietary Difference and Its Effect of the Local Microbiome

1.2.4.1 Asia

Dietary habits in Asia are often influenced by rice consumption, which is widely cultivated in Southeast Asia. Other than rice, there is a large diversity of food depending on the agricultural activity within the region [134–136]. While interstate trade supplements domestic production, the main dietary denominator remains in the regional agricultural activities [137]. On top of this, many developing countries in Asia have governmental recommended dietary allowances (RDAs) that also influence eating habits. A study conducted in Zhejiang, China, showed that the mean daily nutrient intake by urban women met the national RDA, meeting the required levels of macronutrients (energy, carbohydrate, protein, and fat). The Chinese government regulates the national food supply to ensure that each state receives foods that meet the nutritional requirements [138].

Additionally, fermented foods that are rich in prebiotics and probiotics are heavily consumed in Asia-Pacific countries. Such local foods include tempeh, tempoyak (Southeast Asia), natto (Japan), and fermented tea (China and Taiwan); and influence the gut microbiota. Asia-Pacific children are noted to have higher *Bifidobacteria* abundance [139], due to supplementary fermented foods in the diet such as Japanese fermented milk products and Korean kimchi [140, 141].

1.2.4.2 Europe

Due to extensive animal-based husbandry in Europe, tight regulations are enforced to control the release of anthropogenic greenhouse gas emissions (GHGEs) accounting for 25% of total GHGE in Europe [142, 143]. Even so, the

main agricultural produce in Europe is red meat and dairy products [144, 145], thus making red meat (processed and unprocessed) and dairy products as part and parcel of the integral diet in Europe. This led to a subtle change in the Western/European microbiome often showed a higher abundance of *Prevotella* and *Bacteroides* than Asia-Pacific microbiome that favors *Actinobacteria* [146].

1.2.4.3 Australia

The Australian continent agricultural activity focuses on producing wheat, barley, canola, chickpeas, and oats in the winter while producing sorghum grain in the summer. On top of this, other agricultural activities are focused on farming sugarcane, leaving limited farming grounds for orchards and vegetables. This results in lower consumption of fruits and leafy vegetables that are a rich source of prebiotics [147]. Australian diet is also heavily influenced by meat and dairy products [148]. This leads to close to 20% of the adult population being classified as obese as reported by the WHO in 2012 [149, 150]. It is possible that the dietary pattern influenced the increased incidences of *Clostridium difficile* infection and increased rates of ulcerative colitis (UC) observed in Australia [151]. Additionally, it was found that the dairy-rich diet in children also influenced enriched *Firmicutes*-affiliated and *Bifidobacterium* lineages [124].

1.2.4.4 Africa

The geographic location of the African continent results in limited access to proper nutrition among individuals. These are further complicated by years of poverty and geopolitical issues within the continent that prevents agricultural activities in the region. For instance, a study of the populations in the North West Province, Southern Africa, showed barely adequate energy and protein intake and low micronutrient intake among the general population. This includes limited access to green vegetables and fruits that are probiotic-rich needed to cultivate a healthy microbiome [152]. It was also found that children in Africa showed a lower *Firmicutes/Bacteroidetes* ratio and low abundance of *Enterobacteriaceae* (*Shigella* and *Escherichia*) [153]. The dominant genera of *Bacteroides* of African children comprise xylan- and cellulose-degrading microbes (*Prevotella* and *Xylanibacter*) that assist in the digestion of fibrous foods found in tubers like yam and sweet potatoes that are present in the rural African children diet.

1.2.4.5 South America

South America adopts a wide variety of dietary patterns. The primary source of polysaccharide in South American diet includes wheat, corn, rice, and tubers. Yucca and bananas are also part of the daily diet in most Latin American countries. Access to a sugar-rich diet, and low administrative tax on sugar-sweetened products resulted in quicker absorption of energetics in the human body [154]. This impacts pre-adolescents and teenagers, in particular, who were in Latin America have shown an estimated overweight prevalence of approximately 7% in children younger than 5 years. This is further complicated by the high intake of cookies, dairy products, and fruit juices [155, 156].

1.2.4.6 North America

Similar to certain Asian diets, the dietary habit of North Americans is regulated by public health policies [157]. Based on this, the Diet Quality Index was used in evaluating trends of the US population and found significant improvements from 1965 to 1991 [158]. This is further promoted by the Alternate Healthy Eating Index 2010 [159]. It was found that North Americans have a border range of dietary factors, broad macronutrients, multiple food sources, and nutrients [160]. It was shown that US adults consumed more grains from a study conducted from 1999 to 2012, with a stable intake of unprocessed red meat and poultry consumption. Despite the access to a large variety of foods, it was found that the US adults have the least diverse fecal microbiota, showing an abundance of 23 groups (an average non-US adult have 73 groups) with the major constituent in the *Prevotella* genus [161].

1.3 Dietary Modulation of Microbiome for Disease Treatment

In subchapter 1.2, the role of dietary habits and the nutritional composition evidently play a role in both short-term regulation of the microbiome and long-term shaping of the microbiota landscape [54, 96, 162]. The microbiome changes facilitate various health-benefiting properties to the host, such as regulating the host immune system, perturbing host growth, and development, altering the host biochemistry and affecting the microbiome in other parts of the human host [163, 164]. It is often unclear whether it is the change of the host biochemistry that perturbs the microbiota population or the changes of the microbiota population that alters the host biochemistry (Figure 1.4). However, certainly these changes can positively influence the hosts' health by boosting the immune system or negatively impacting the host through dysbiosis, resulting in the pathogenesis of various diseases. Through shaping the host's dietary pattern, it is possible to encourage the growth of the desired microbiota population through the use of prebiotics and nutrients or to eliminate antagonistic competitors of the health-conferring commensals using probiotics.

1.3.1 Infection

Infections in the human host occur resulting from microbiome dysbiosis, where there is a change in the interactions between the various members of the microbiota and the human host cells. These changes can be transient and may restore to a state of equilibrium as the host recovers from the ailment or might result in a permanent perturbation that results in an altered microbiome state. The following section will look at the various dietary-related approaches used to restore balance in the microbiota.

1.3.1.1 Fecal Microbiota Transplantation (FMT)

The concept of fecal microbiota transplantation (FMT) is to import the colonic microbiome from a healthy person, and transferring it to the intestine of a



Figure 1.4 Dietary perturbation of the microbiome to improve human health. The healthy microbiome results from an equilibrium of host biochemistry and its microbiota (a). During dysbiosis, the population of certain disease-causing microbes increases, resulting in pathogenesis (b). Using diet, it is possible to help restore balance in the host biochemistry and establish a balanced microbiota in the host. This can be achieved using prebiotics, probiotics, and nutrition to perturb the host microbiome (c). However, sustained dysbiosis will result in disease pathogenesis, resulting in the manifestation of the disease symptoms (d).



Figure 1.5 Protocol of FMT. Stool from healthy donors are screened and tested. The acceptable stool is homogenized and filtered to obtain stool slurry [165]. Fecal suspensions were given via oral capsules, through nasogastric and nasoduodenal tubes into the upper gastrointestinal tract (top), or through a colonoscope or a retention enema catheter into the colon (bottom). Source: Based on Bakken [166].

diseased patient to restore the microbiota (Figure 1.5) [165-167]. FMT is used in the treatment of *Clostridium difficile* infection (CDI), IBD, insulin resistance, and other diseases [168]. In this section, we will discuss the role of FMT in tackling CDI.

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CDI results from excessive use of antibiotics or gastrointestinal surgery, resulting in the loss of the local microbiota. Such local microbiota includes the loss of essential groups from the *Lachnospiraceae* and *Enterobacteriaceae* communities. These changes in the structure and functions of the resident microbiota reduce the resistance for intestinal pathogens, such as *Clostridium difficile*, to localize and propagate in the gut [169, 170]. While other pathogens can be treated with other antibiotic treatments, *C. difficile* can exist in three different lifestyles (planktonic, biofilm, and spore) that complicate the process of eliminating these pathogens from the gut. The ability of the microbe to evade antibiotic treatment by regulating its lifestyle often leads to recurrent CDI, where the intestinal microbiota fails to recover and thus establishing a new homeostatic balance within the host post-initial insult. Left untreated, the pathogen can manifest in different forms including diarrhea, pseudomembranous colitis, toxic mega colon, and other symptoms, even rarely resulting in death [171, 172].

Tremendous amount of research links bacterial dysbiosis in both human and mice showed the depletion of *Bacteroidetes* and enrichment of *Proteobacteria* that are linked to a higher risk rate of acquiring CDI [173–176]. The use of FMT to treat CDI showed lower rates of recurrent CDI, leading to the recovery of the *Bacteroidetes* and *Clostridium* clusters IV and XIVa (*Firmicutes*) while showing depletion of the *Proteobacteria* populations [177, 178]. This is further proven by a study conducted on 317 patients showing 92% of patients showed complete recovery from CDI, out of which 89% exhibited full recovery after the first treatment. Only approximately 4% of patients experienced a relapse in symptoms after the FMT [177, 178]. It is mentioned from the studies above that FMT as adjunctive therapy to antibiotic treatment would be an avenue that merits further investigation.

Aside from typical colonoscopic lavage, there is increasing interest in oral delivery of encapsulated FMT. Compared to colonoscopy, oral FMT administration is considered non-invasive, less resource intensive, easily administered, and more accessible to patients [179]. A meta-analysis has identified that a single FMT capsule infusion has an average colonization efficiency of 80%, whereas multiple infusions showed 92% efficiency [180]. In a randomized clinical trial, orally administered FMT showed minimal difference compared to FMT lavage to prevent recurrent infection over 12 weeks [181]. Current studies are geared toward developing smart oral delivery methods to facilitate the targeted release of the microbes. Preliminary studies of FMT capsules with a targeted colonic release (FMTcr) showed better therapeutic effects compared to FMT capsules with the gastric release (FMTgr) [182].

1.3.1.2 Prebiotic-, Diet-, and Probiotic-Mediated Prevention of Pathogenic Infections

As discussed in the earlier subchapter 1.2, a perturbation in the gut ecosystem increases the risk of microbiome dysbiosis, significantly increasing the hosts' vulnerability to infection [163, 183]. Thus, other measures have been taken to re-establish homeostatic balance and restore the host health. In the following, we will discuss the use of prebiotics, diet, and probiotic means of balancing the gut microbiome.

The use of prebiotic fibers has been proven to increase the localization of *Firmicutes* and *Bacteroidetes*. Studies using a non-Westernized diet (balanced fat, sugar, and dietary fiber) found that the microbiota stability was maintained better than those with a Western diet when challenged with antibiotic treatment, preventing the proliferation and colonization of opportunistic pathogens [184]. In a separate study, mice fed with microbiota-accessible carbohydrates (MAC) were shown to mitigate CDI through promoting the growth of MAC-utilizing taxa, resulting in the production of beneficial metabolites such as SCFA [185].

Adjusting the dietary consumption of lipids was further found to encourage the growth of certain microbial groups by altering hepatic lipid and bile metabolism, thus indirectly changing the microbiome and their corresponding metabolites [163]. Fatty acids can alter pathogen virulence, survival, and growth; thus, clinical applications of fatty acid in infection treatment are carried out [186]. Scientists studying various dietary lipid sources influence the host's pathological response to *Citrobacter rodentium* infection, where olive oil showed one of the best chemoprotective properties [187].

1.3.2 Inflammatory Disease

In the event of microbiome dysbiosis, inflammation occurs resulting from the immune system attempting to remedy the situation [188]. There are increasing evidences suggesting the link of diet, microbiota imbalance, and the pathogenesis of the inflammatory disease. The nutritional composition may trigger inflammation through direct interactions with the mucosal tissues and indirect interactions by altering the microbiota composition [164, 189–192]. We will discuss IBD as a case study on the effect of diet on IBD pathogenesis.

Patients suffering from IBD experience due to long-term incidences of tissue inflammation on the dorsal end of the GI tract [193] that can be divided into Crohn's disease (CD) and UC. The dietary habits of individuals can either prevent or increase the risk of developing IBD [193]. A westernized diet abundant in fat and protein increases the risk of developing IBD [194], while fiber-rich diet was found to lower the risk of developing IBD in rats [195, 196]. As discussed in Section 1.2, a fatty and protein-rich diet was found to enrich *Proteobacteria* and deplete *Firmicutes* and *Bacteroidetes* involved in the biosynthesis of butyrate production [197–199]. These reduced levels of SCFAs in the large intestine are primarily attributed to preventing bowel inflammation [200, 201]. The use of FMT to enrich butyrate-producing microbes was found to recover the microbiome balance and alleviate IBD symptoms.

There are various approaches to treat CD, where the use of exclusive enteral nutrition (EEN) [164, 191] has been used as first-line therapy to treat pediatric patients in some countries and regions [202, 203]. A study involving 114 CD patients below the age of 12 showed an approximately 88% remission rate when subjected to EEN [204]. Another study compared oral and continuous enteral feeding of EEN to alleviate symptoms in both groups [205]. The mechanism of EEN-induced CD remission is unclear where a variation of EEN showed that the composition does not play a direct role in the recovery process [164]. It is

hypothesized that EEN triggers anti-inflammatory molecule production, intestinal barrier restoration, and recovers microbiota perturbation [191, 206]. It was found that EEN decreases microbiome diversity, triggering enrichment of certain populations in the microbiota [207–209]. Despite variations in the enriched population, EEN does certainly affect the microbiota populations and in turn change the microbiome landscape.

Other nutritional elements such as amino acids, fibers, vitamins, and fatty acids can influence IBD pathogenesis. Some studies showed that glutamineand arginine-supplemented diet conferred improved protection against dextran sulfate sodium (DSS)-induced colitis in a murine model [210, 211]. Prebiotic fibers can attenuate IBD symptoms in mice model [195, 212] through regulating intestinal bacterial composition and synthesis of anti-inflammatory by-products, such as SCFAs [193, 213, 214].

1.3.3 Cancer

Many studies concluded that the microbiota plays a role in cancer pathogenesis in humans. It is further demonstrated that the dietary nutritional content facilitates the behavior of the microbiome. Prebiotics-containing fiber (soluble and insoluble) helps to move the bowel by bulking up the intestinal lumen and absorbing carcinogens such as nitrosamines, thus limiting the contact time of the carcinogens to the GI epithelium tissue. These fibers also house the SCFA-producing microbes, enriching the Gram-positive anaerobic *Firmicutes* population and providing the substance for microbial fermentation [215–218]. The two most abundant butyrate-producing *Firmicutes* in the human colon are *E. rectale/Roseburia* spp. and *F. prausnitzii. E. rectale/Roseburia* spp. belongs to the *Clostridium coccoides* (or Clostridial cluster XIVa) cluster, and *F. prausnitzii* belongs to the *C. leptum* (or Clostridial cluster IV) cluster [219–222].

The SCFA butyrate can prevent gut tissue inflammation and suppress cancer cell motility by deactivating Akt/ERK signaling pathway of histone deacetylase in colorectal cancer and lymphoma cancer [223]. Butyrate also exerts its anticancer activity by interfering with the mitochondrial and exogenous apoptotic pathways through regulating oncogenic signaling molecules through microRNAs and methylation [224, 225]. On top of generating butyrate, these bacteria can produce other metabolites such as lactic acid and formic acid that can further exert anticancer activities [226].

Cruciferous plant-rich diet was also found to help in the prevention of colorectal cancer. Cruciferous vegetables are enriched with glucosinolates, a precursor to the anticancer agent isothiocyanates. These glucosinolates require to be catalyzed by the enzyme myrosinase to form its isothiocyanate derivatives. A study showed that cruciferous-rich and fruit-rich diet enriches certain groups of *Actinobacteria, Firmicutes*, and *Bacteroides* that have weak myrosinase-like properties [227]. Other approaches to augment the myrosinase activity were achieved using engineered microbes such as *E. coli* Nissle 1917 [228]. Other means of dietary regulation also reduce the risk of developing cancer by the displacement of pathogens associated with cancer pathogenesis. Colon cancer patients were found to have an enriched population of *Fusobacterium nucleatum*

compared to healthy test subjects detected in both colorectal biopsies and patient stool samples [229–233]. *E. nucleatum* from the phyla *Fusobacteria* is a Gram-negative non-spore-forming bacilli that is strictly anaerobic and is usually found in the mouth, playing a role in various diseases such as periodontitis, appendicitis, gingivitis and invasive infections in the other organs. Studies showed that *F. nucleatum* exerts the cancer pathogenesis through the interaction of three biomolecules located on the surface of the microbe: lipopolysaccharide (LPS), adhesin A (FadA), and fusobacterium autotransporter protein 2 (Fap2) [234]. Fiber-enriched and low-fat diet can reduce the risk of *F. nucleatum*-positive colorectal cancer through the displacement of the pathogen from the gut; however, the dietary change does not show any significant improvements in *F. nucleatum*-negative cancer patients [235]. These studies suggest the role of diet pattern in displacing *F. nucleatum*, thus negating the risk of colorectal cancer development, showing the relationship between diet, microbiome, and cancer pathogenesis.

1.3.4 Psychological Disease

Increasing studies on the brain–gut–microbiome (BGM) axis describe the bidirectional interactions between the central nervous system, gastrointestinal tract, and gut microbiota [236, 237]. Increasing evidence has proposed that this axis contributes largely to pathologies of some psychological diseases, such as autism spectrum disorder (ASD) [237, 238], Parkinson's disease (PD), and Alzheimer's disease (AD) [239, 240]. This section will discuss the dietary effects on ASD and neurodegenerative diseases.

1.3.4.1 Autism Spectrum Disorder

ASD is a neurodevelopment disorder that influences the social behavior and communication of afflicted individuals throughout their lifetime [241, 242], where ASD severity is linked to the intestinal microbiota and gastrointestinal symptoms [238, 243]. Studies on isolated fecal bacteria from ASD patients revealed microbial dysbiosis resulting in the enrichment of *Clostridium*, *Lactobacillus*, and Desulfovibrio species; and decreased Bacteroidetes/Firmicutes ratio [244–247]. Carbohydrate-degrading bacteria from the Prevotella, Coprococcus, and unclassified Veillonellaceae genera showed lower abundance than healthy people [248]. Despite this observation, the fluctuations of specific bacterial species from different studies are inconsistent, thus proving a challenge to determine the role of bacteria dysbiosis in the pathogenesis of ASD [238]. Clinical research using specialized diet to alleviate ASD symptoms has been studied to perturb these microbiota populations. Gluten- and casein-free (GFCF) diet is currently widely prescribed to children with ASD, designed to reduce leaky gut-causing proteins and facilitate symptom remission [249]. However, there are some inconsistencies in treatment in some small clinical trials [250-252]. Alternatively, the ketogenic diet was found to improve ASD symptoms both in an animal model and small-sized clinical experiment despite potentially causing ketosis. This is due to the ketogenic diet to compensate the lower Firmicutes to Bacteroidetes ratio and increase A. muciniphila in mice of ASD [253]. While showing much success in

mice, the detailed mechanism linking in a ketogenic diet, gut microbiota, and ASD remains unclear due to the lack of appropriate animal models that mimics the human BGM [254]. In addition to altering dietary composition, probiotics, such as *Lactobacillus* and *Bifidobacterium*, have been found to improve ASD behavior while treating the ASD-linked gastrointestinal symptoms [255, 256].

1.3.4.2 Neurodegenerative Diseases

Neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) were found to be exacerbated by the disruption in gut microbiota, contributing to the pathogenesis of neurodegenerative disorders via the BGM [239, 257]. PD patients were reported to observe an increase in genus Lactobacillus, Bifidobacterium, and Akkermansia (pro-inflammatory, mucin-degrading Gram-negative bacteria) population, and a decrease in the Faecalibacterium, Coprococcus, Blautia, Prevotella, and other microbes of the Prevotellaceae family (the bacteria responsible to SCFA production) [258, 259]. Dietary supplementation of specific probiotics, such as Lactobacillus and Bifidobacterium, was found to treat neurodegenerative symptoms in clinical trials and mice [260-262]. Phytochemicals, such as caffeine from ingested coffee and tea, were found to have an inverse relation, lowering the risk of developing PD. [263] It was also shown that caffeine confers neuroprotective properties in PD-induced mice models [264, 265]. Similar to ASD, a ketogenic diet was identified to improve symptoms of PD and AD both in animal models and clinical trials [266-270]. These results indicate the role of diet in regulating the microbiota population involved in preventing neurodegenerative disease.

1.3.5 Metabolic Disorder

Metabolic disorders are caused by the dysbiosis of intestinal microbiota, resulting in changes in the host's ability to digest certain types of foods. This leads to various disease metabolic disorders such as obesity, diabetes, and non-alcoholic fatty liver disease (NAFLD). In this chapter, we will discuss these metabolic disorders and their link to diet and the microbiome.

1.3.5.1 Obesity

The gut microbiota composition affects the host's ability to digest different types of food, thereby causing the host to metabolize the nutrients from the food itself. In 2004, a group determined that the gut microbiota regulates lipid storage in the human body [271]. Later in 2006, they found significant differences between the relative abundance of *Bacteroidetes* and *Firmicutes* in the GI tract of obese and lean mice. The study also reported that FMT of samples from obese mice to germ-free mice resulted in the development of obesity pre-symptoms [131]. The same research group further studied the GI microbiota from monozygotic and dizygotic twins with different weight groups (lean and obese) and discovered large variations in the gut microbiota despite having similar genetic makeup [45]. The research team then conducted FMT of microbiota from the identical twins into germ-free mice. Groups provided with FMT from lean donors maintained

normal weight, while groups treated with FMT from obese donors gained a significant amount of weight throughout the study [272].

The role of gut microbes in regulating fat storage in their human host is mainly attributed to the ability of these microbes to ferment complex polysaccharides that the host generally cannot absorb from the diet [273]. Microbes such as *B. thetaiotaomicron* have been shown to induce the expression of monosaccharide transporters in mice [274], where the polysaccharides are hydrolyzed into monosaccharides and SCFAs for easy absorption by the host intestinal cells. The increase of sugar uptake is then converted to lipids in the liver, triggering intestinal microbes to facilitate host expression fat metabolism gene *Fiaf* resulting in the accumulation of excessive fat [275]. Other studies have shown that orally introduced probiotics in mice fed with a high-fat diet prevent the perturbation of intestinal mucosal permeability and limit energy absorption. These oral probiotics exert such bioactivity by reducing plasma LPS and cytokines and promote the gut secretion of glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2) involved in maintaining the intestinal mucosal barrier [276].

1.3.5.2 Diabetes

Diabetes is a metabolic disorder that results in an increased sugar serum level, often resulting from the deficiency of insulin secretion or insulin insensitivity. Studies have shown that bacterial abundance in the gut has a strong correlation to the onset of diabetes. This has been shown in type II diabetes (T2D) patients that showed increased Firmicutes abundances with a proportional decrease in Bacteroidetes abundance. Long-term observation of T2D patients undergoing weight loss showed a recovery of Bacteroidetes abundance and depletion of Firmicutes population [131]. It was discovered that the ratio of GI Firmicutes/Bacteroides affects the body metabolism, where patients with higher ratio were shown to be more susceptible to inflammatory responses, increased BMI, and a higher risk of developing insulin resistance that may lead to type 2 diabetes [271, 275, 277]. Certain studies indicated that orally administered prebiotics helps lower the ratio in hyperphagic, obese, and hyperglycemic mice model (ob/ob), which caused an increase in the number of L-cells [278]. The increase of L-cells raises the plasma levels of GLP-1, triggering glucagon expression, resulting in leaner mice compared to the untreated groups.

1.3.5.3 Non-alcoholic Fatty Liver Disease (NAFLD)

NAFLD is a metabolic disorder that results from the build-up of liver fat in patients without a history of impaired liver function from heavy drinking, viral infections, or other liver diseases [279, 280]. NAFLD is the most common liver disease globally, with the number of patients increasing annually. Studies have found that the prevalence of NAFLD is linked to gut microbiota, where patients with liver failure often observe microbial overgrowth of small intestinal and are used as an indicator to determine the liver failure severity [281]. As discussed earlier, the ratio of *Firmicutes/Bacteroides* affects the host insulin resistance. On top of that, the ratio affects increasing endogenous ethanol production and inducing choline deficiency in the host increasing the risk of NAFLD development [282]. Ethanol produced by the microbiota increases intestinal

mucosal permeability that coupled with choline deficiency, triggers the toll-like receptors, which stimulate hepatocytes to produce plentiful cytokines involved in NAFLD pathogenesis [283].

Prebiotics and lactulose are commonly used to treat NAFLD enriching the *Bifidobacterium* abundance. Other prebiotics from the inulin-type fructose fed to NAFLD animal models were shown to reduce the development of hepatic steatosis. These oligofructoses reduce fatty acid synthesis, promote weight loss by regulating intestinal polypeptides, reducing inflammation and proinflammatory cytokines, improving blood sugar regulation, and regulating intestinal microbiota [281, 284].

1.4 Challenges and Opportunities

1.4.1 Limitations in the Field

While we have observed great strides in microbiome research, there are many more aspects that would need further investigation. Currently, most studies focus on the effects of the single nutrient and its role in modulating microbiota. However, human dietary habits are complex, where synergistic effects of nutrients might need to be further investigated. Further, a larger cohort of long-term human microbiome studies would be needed to map and predict the shift in the microbiome. This would include the role of dietary and socio-economic impacts on the human host [96]. Additionally, further studies linking diet and daily activities would be needed. Studies suggest higher gut Shannon index in individuals who regularly exercise and practice good dietary habits compared to sedentary individuals [285]. Thus, further research would be merited to understand better the role of microbiome, diet, and human health.

1.4.2 Current Microbiome Project Supporting Infrastructures

The US NIH initiated the research on the human microbiome that triggered a global effort in this field. In 2008, the International Human Microbiome Consortium (IHMC) was established to set up globally accepted policies and coordinate international microbiome initiatives, including those in the EU, US, China, Japan, Singapore, Australia, and Canada. Table 1.5 shows the current supporting agencies in different countries.

1.4.2.1 International and Local Initiatives

The established infrastructures kickstarted various local and global initiatives to accelerate microbiome research. These include databases and research platforms founded by universities, research institutions, and major corporations. These initiatives study diverse research work, focusing on particular human societal niches. Listed below are some of such initiatives.

• HMP [286]: The first-phase HMP (HMP-1) (2008–2013) is a concerted global effort that investigates samples of donors and studying the microbiome

Countries	Supporting agencies
Australia	Commonwealth Scientific, Industrial Research Organisation, National Health and Medical Research Council
Canada	Canadian Institutes of Health Research, Genome Canada
Europe	European Commission
France	Institut National de la Recherche Agronomique
Gambia	Medical Research Council
Germany	European Molecular Biology Laboratory
Ireland	Teagasc Moorepark Food Research Centre, University College Cork
Japan	Japan Science & Technology Agency, JST, Ministry of Education, Cultures, Sports, Sciences and Technology, MEXT
Kazakhstan	Nazarbayev University
Korea	National Research Foundation, Korea Research Institute of Bioscience and Biotechnology (KRIBB)
United States of America	National Institutes of Health (NIH)
China	Institute of Microbiology, Chinese Academy of Sciences

 Table 1.5 Infrastructures supporting microbiome research.

of 15–18 sites of the human body. These microbial taxonomic profiles and metagenomic sequences, described in the form of abundance, lay the foundations for the HMP-2.

- HMP-2: The second phase of the HMP, also known as the integrated HMP (iHMP), uses the Data Analysis and Coordination Center (DACC) platform to facilitate rapid data retrieval of metagenomic sequence and other data types of the human microbiome and human genetics.
- METAgenomics of the Human Intestinal Tract (MetaHIT): MetaHIT (2008–2012) is a European Union initiative that links 15 institutes from 8 countries, providing a multi-disciplinary and extensive catalogue of microbiome resilience potential in the human body [287]. MetaHIT was succeeded by the Horizon2020 (2014–2020) that advances research in microbiome nutrition and host health.
- The Microsetta Initiative (TMI): TMI consolidates the global efforts of profiling the microbiome of collected human samples from across the globe, including educational outreach of microbiome sciences [288]. TMI is the human microbiome research wing of the Earth Microbiome Project.
- Million Microbiome of Humans Project (MMHP): Launched at the 14th International Conference on Genomics (ICG-14) in 2019 [289], the MMHP is global cooperation between scientists from China, Sweden, Denmark, France, Latvia, and other countries studying microbial metagenomics research. This project aims to sequence and profiles the microbiome of one million samples isolated from the human body, to ultimately construct a complete human

body microbiome map and build the world's largest human microbiome database using MGI's DNBSEQ[™] metagenomic sequencing [290].

 Bioinformatic initiatives: The most prominent bioinformatic initiative is the DACC [291] that plays a crucial role in iHMP. The Global Catalogue of Metagenomics (gcMeta) is another bioinformatics platform that archives microbiome data while facilitating data standardization and analysis [55].

Various governments and their affiliated health institutes have initiated many national-level microbiome projects to encourage microbiome research. In Ireland, the government-funded Metagenomics of the Elderly programme (Elder-Met) investigates the relationship between diet, gut bacteria, and health status in the elderly [292]. The Canadian Institutes of Health Research (CIHR) launched the Canadian Microbiome Initiative (CMI) in 2014 aiming to analyze and characterize the microorganisms that colonize the human body in an effort to harness the microbiome for treatment of chronic disease [293]. In 2017, the second phase of CMI was launched, aiming to develop effective preventative and therapeutic interventions through a deeper understanding of the causational role of the microbiome in human health and disease. The Japanese Human Metagenome was established to study the gut microbiome of healthy Japanese and its microbial diversity, comparing with metagenomic data from HMP [294].

1.4.2.2 Global Foundations

Many multinational companies have jumped into the foray to help push forward microbiome research. These foundations are listed below:

- Bill and Melinda Gates foundation has supported 34 institutes/initiatives on the microbiome research, from 2008 to the current day.¹
- The Biocodex Microbiota Foundation provides an annual grant of €200,000 for research on the structure of microbiota and the impact of microbiota dysbiosis [295].
- The Crohn's & Colitis Foundation has raised over \$250 million toward the global IBD research [296].
- The W. GARFIELD WESTON foundation has set up the Weston Family Microbiome Initiative providing research grants of up to \$200,000 on microbiome translational research to improve the health of Canadians [297].
- Wisconsin Alumni Research Foundation (WARF) supports projects on gut microbiome–linked Alzheimer's disease, the impact of day care on a child's microbiome, and the risk of infection with drug-resistant pathogens [298].

1.5 Concluding Remarks

There is an undeniable link between the microbes that live in the human body with the human host. The microbes and the human host forming the microbiome, establish the individual's health where the microbial composition changes over the age of the host and the biochemical conditions of the host. One of the main

¹ Bill and Melinda Gates foundation.

determining factors of the host biochemistry is the host diet, where foods can affect how the host cells and the microbiota reacts.

In this chapter, we compare different impacts of diet primarily based on wealth, age, and locality. From a socio-economic standpoint, wealth influences the eating and lifestyle habits of individuals and in doing so impacts the microbiome. The age influence is mainly due to the differences in consumed nutrients composition affecting the microbiota of infants, children, teenagers, adults, and elderlies. In contrast, the locality provides different types of food, affected by geography, climate, and customs. Thus, we can observe differences in health levels in different countries. It is considered that wealth also influences diet choice and risk of some diseases, mainly because people with different levels of wealth may have different views on the consumption of foods (such as probiotics) and living habits.

Designed diets are currently used to treat or prevent diseases, by controlling the amount of specific dietary components, probiotics, and prebiotics. These treating strategies have been explored in infection, inflammatory diseases, psychological diseases, cancers, metabolic disorders, and other diseases. The changes in the diet affect intestinal epithelial cells and intestinal barrier function as a direct means of interaction with the host. Dietary changes can also influence the microbiota composition, mainly by repressing pathogenic bacterium and promoting the growth of beneficial bacteria. The change in microbiota composition can also influence host immunity. Thus, the diet components that encourage specific species of microbes as means to control disease pathogenesis are currently investigated.

These researches are being supported by various governmental, Non-Governmental Organizations, and private institutions, indicating the importance of the field. It is clear that the role of diet indeed is an important aspect of host health and would merit further investigation.

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