

Diet and the microbiome in precision medicine

Miguel Toribio-Mateas^{1,2} and Adri Bester¹

¹*Bowels and Brains Lab, School of Applied Science, London South Bank University, London, United Kingdom;* ²*School of Health and Education, Faculty of Transdisciplinary Practice, Middlesex University, London, United Kingdom*

Interactions between microbiome, health, and disease

The role of the gut flora in health and disease is as crucial as it is complex. Ample evidence from both human and animal studies describes the impact of dietary interventions on the idiosyncrasies of the gut microbiota, the tens of trillions of microorganisms [1,2] that inhabit our gastrointestinal system, in quantities, and diversity increasing from stomach to small intestine to colon [3,4].

Under natural conditions, intestinal bacteria share their habitat with a dynamic community of viruses, protozoa, helminths, and fungi [5–7], many of which exhibit parasitic behavior [8]. Every unique community of microorganisms interacts with their human host, through immune, neuroendocrine, and neural pathways [9], thereby casting local as well as systemic effects on the host's health, as well as disease risks. In fact, alterations in normal commensal gut microbiota result in an increase in pathogenic microbes, which deranges both microbial and host homeostasis.

Consumption of ultraprocessed foods is considered to lead to the microbial imbalance known as dysbiosis, that has been widely reported as a key contributor to the multiple system dysregulation, observed in the pathogenesis of cardiovascular [10–12], metabolic [13–16], neuroimmune [17–20], and neurodegenerative [21–24] conditions.

A recent review by Valdes et al. [25] provides a succinct yet comprehensive summary, of the role of the gut microbiota in nutrition and health, analyzing various popular food-based interventions such as low FODMAPS, polyphenol-rich diets, etc., and correlates them with microbial diversity and health. Nutrients in food are sources of information, so the cross talk between the host microbiome and their epigenome is also of paramount importance. This is beautifully depicted by Qin and Wade [26] and expanded

on by Prescott et al. [27], from an angle that takes into consideration the interconnected web of biological responses. The input is based on the total exposures to factors that interact epigenetically with the microbiome and its host over time, otherwise known as the human exposome.

In practical terms, this means that when practitioners assess an individual's clinical presentation, they should consider how their lifestyle might be contributing to the composition and the functionality of their gut microbiota, and vice-versa. Seeing the person through a wide-angle lens helps clinicians account for environmental as well as psychosocial exposures as forces that, according to Prescott et al. [27], “operate collectively and cumulatively, to increase the burden of chronic disease.” As food choices do not exist in isolation, practitioners with a whole-person approach should be mindful of other factors such as trauma or stress, relationships, sleep, and movement, when working with their patients.

Western diets and microbiota composition

Microbiota composition analyses of Western diets tend to report narrower bacterial diversity, along with altered microbial profiles, when compared with a Mediterranean dietary pattern [28]. It is worth remembering that Western diets are not just “high in fat” or “carbohydrate-rich,” as they are often described. They feature a variety of what the NOVA food classification [29] defines as “ultraprocessed foods,” i.e., hyperpalatable, “energy-dense, high in unhealthy types of fat, refined starches, free sugars and salt, and poor sources of protein, dietary fiber, and micronutrients” [30]. Typical ultraprocessed food items are fizzy drinks, margarines and spreads, cookies, biscuits, breakfast cereals, energy bars, energy drinks, prepared pies, pizzas, meat nuggets, and prepackaged or “ready meals,”

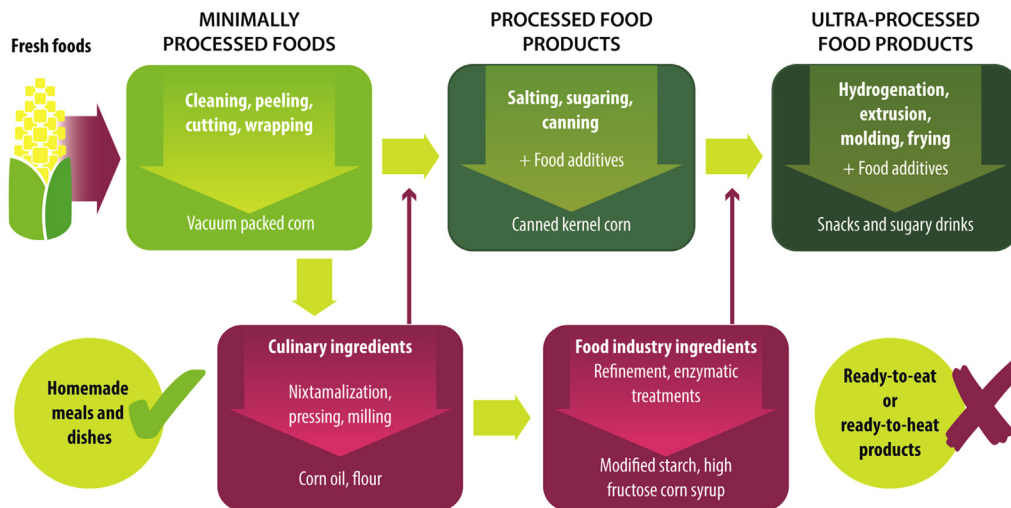


FIGURE 43.1 Industrial processing stages, from fresh food to ultraprocessed food products. Reproduced with permission Aguayo-Patrón, S.V., Calderón de la Barca A.M. Old fashioned vs. Ultra-processed-based current diets: possible implication in the increased susceptibility to type 1 diabetes and celiac disease in childhood. *Foods* 2017;6:100. Licence information: Image appears in *Foods*. 2017 Nov 15;6(11). pii: E100. <https://doi.org/10.3390/foods6110100>. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).

containing large amounts of saturated and trans fats along with sucrose, emulsifiers, sweeteners, and high glycemic carbohydrates, e.g., maltodextrin, while offering little micronutrient value, as seen in Fig. 43.1.

Demonizing individual food items is not particularly helpful clinically. However, it is now known that dietary emulsifiers are able to alter the mucus layer thickness, thereby affecting the interactions between gut microbes and host cells [31], and mediating increased levels of proinflammatory lipopolysaccharide (LPS) [32]. Sweeteners have been shown to induce metabolic aberrations mediated by alterations in gut microbiota in animal models [33] and are known to reduce microbial diversity in humans [34], leading to altered glucose homeostasis, decreased satiety, increased caloric consumption, and weight gain [35].

Sweeteners can also affect cognitive processes such as memory, reward learning, and taste perception [36], all of which can affect an individual's relationship with food, as well as food choices [37]. Interestingly, a Western dietary pattern has been seen to affect autonomic regulation and vagal cardiac activity [38], and reduced heart rate variability—a sign of autonomic dysregulation—has been seen in individuals suffering from strong attachment to hyperpalatable foods, which some authors refer to as “food addiction” [39,40].

The mediterranean diet pattern as a source of richness and diversity

A growing number of studies of good methodological quality continue to provide substantiation for the ability of the Mediterranean diet (MD henceforth), to effect positive

changes in gut microbiota composition and diversity. On that basis, it is proposed that an MD pattern provides a reliable answer to the question of what “a healthy diet for the microbiome” might be. Gut microbiota and metabolome analysis of 51 vegetarians, 51 vegans, and 51 omnivores, distributed across four geographically distant cities in Italy, was conducted by De Filippis et al. [41]. Adherence to the Mediterranean dietary pattern represented a vital factor, contributing to the wider diversity of their gut microbiota. The 11-unit dietary score by Agnoli et al. [42] was employed, and the diversity and abundance of “healthy foods” such as brightly colored vegetables, fruit, nuts, and minimally processed cereals consumed by participants was characterized using the Healthy Food Diversity (HFD) index by Drescher et al. [43]. Participants with the highest adherence level to the MD along with the highest HFD scores presented with highest levels of fecal short-chain fatty acids, irrespective of whether their diets included specific food items such as meat, fish or dairy, etc. [41].

In the authors' own clinical experience, using a practical tool such as the “50-food challenge” data collection chart (please see Fig. 43.2) [9] can help boost patients' creativity around food choices, thereby promoting engagement with the concept of dietary diversity, and optimizing compliance.

As another taster of the ample evidence substantiating the MD's beneficial effect on the gut microbiota, in a transversal study of 31 adults without a previous diagnosis of cancer, autoimmune or digestive diseases, researchers at the Department of Functional Biology of the University of Oviedo in Asturias, Spain, found that participants with the closest adherence to a Mediterranean-style dietary pattern experienced statistically significant changes in a number of

How varied is your diet?

A varied diet that's rich in colourful foods helps feed a diverse gut flora. Make healthy eating fun by keeping track of every different food you eat for a week and aim for at least 50 foods, all colours of the rainbow, the brighter the better. Red and white onions count as 2 different foods, bread and pasta count as just one, i.e. wheat. Herbs, spices and oils all count as individual ingredients.

Could you have 50 fresh, brightly-coloured foods in a week?

FIGURE 43.2 50-food challenge chart. Reproduced with permission from Toribio–Mateas, M. Harnessing the power of microbiome assessment tools as part of neuroprotective nutrition and lifestyle medicine interventions. *Microorganisms* 2018;6:35. The “50-food challenge” chart is an example of a simple but powerful data collection tool used in clinical practice to engage with patients in a light-hearted way so that they report back to their practitioner on their dietary diversity. The rationale is to motivate individuals to vary the foods they have every day, so that they are increasing their micronutrient diversity, thereby feeding different classes of gut microbes. Licence information: Image appears in *Microorganisms*. 2018 Apr 25;6(2). pii: E35. <https://doi.org/10.3390/microorganisms6020035>. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).

bacterial communities. This included overall higher abundance of Bacteroidetes, Prevotellaceae, and *Prevotella* and a lower concentration of Firmicutes and *Lachnospiraceae*, assessed by 16S rRNA gene sequencing [44].

Adherence to the MD was defined as scores ≥ 4 in the validated Mediterranean Diet Score (MDS) by Trichopoulos et al. [45]. These alterations in gut microbiota richness and spread are consistent with effects of increased dietary fiber from vegetables, legumes, and whole—as in minimally processed—grains, as well as phenolic compounds and carotenoids typically featured in MD foods, such as seasonal and citrus fruits, leafy, pod, and root vegetables, in addition to bulbs, e.g., onions, garlic, leeks, not forgetting red wine and coffee [46,47]. Subjects with an MDS ≥ 4 also had higher concentrations of fecal short-chain fatty acids, butyrate and propionate [44], measured by high-performance liquid chromatography.

The same research team reported a link between dietary bioactive compounds in the MD and the fecal metabolic phenolic profile of 74 healthy volunteers. According to Gutierrez-Diaz et al. [48], participants with median MDS ≥ 4 (based on the MDS by [45]), displayed higher levels of commensal Clostridia belonging to the cluster XVIa, particularly *Faecalibacterium prausnitzii*. This

bundle of microbes from the Clostridia class falls under the Firmicutes phylum and is known for their ability to colonize the mucin layer of human colon, thereby aiding in the maintenance of gut homeostasis [49]. It includes species such as *Eubacterium rectale*, *Papillibacter cinnamivorans*, *Eubacterium ventriosum*, *Butyrivibrio crossotus*, *Clostridium orbiscindens*, *Coprococcus eutactus*, *Roseburia intestinalis*, and *F. prausnitzii*, known to play a major role in mediating the production of butyrate from fermentable dietary carbohydrates [50,51].

F. prausnitzii is considered to have strong anti-inflammatory properties [52]. This is largely mediated by its ability to produce butyrate, thereby protecting the gut mucosa [53], but also by butyrate-independent pathways, which seem to include its ability to block NF-kappaB activation and IL-8 production [54]. Low levels of *F. prausnitzii*, *E. rectale*, and *Eubacterium hallii* have been associated with a peripheral inflammatory state, in patients with cognitive impairment and brain amyloidosis [21].

Low levels of genus *Roseburia* microbes have been seen in patients with primary sclerosing cholangitis and ulcerative colitis [55], as well as in those affected by constipation-predominant irritable bowel syndrome [56]. In the first metagenome-wide study of gut microbiota in type 2

diabetes mellitus (T2D), researchers found that *R. intestinalis* and *F. prausnitzii* concentrations were lower in T2D, compared with healthy individuals [57].

Further thoughts on the Mediterranean dietary pattern

For laypeople, the thought of the MD conjures images of olive oil, vibrantly colorful salads, nuts/seeds, and red wine. For clinicians, the MD is likely to elicit thoughts of large studies like PREDIMED [58]. For researchers, however, the richness in bioactive compounds found in typically Mediterranean foods probably makes the MD as exciting as it is challenging, particularly when trying to match individual dietary components with single clinical endpoints. In fact, the PREDIMED study itself featured myocardial infarction, stroke, or cardiovascular death as a primary composite endpoint [59].

The intervention group consisting of men (aged 55–75) and women (aged 60–80 years), supplementing their diet with extra-virgin olive oil (EVOO) or mixed nuts (walnuts, almonds, and hazelnuts) [60], experienced a 30% reduction in the incidence of cardiovascular events. How much might the gut microbiota of participants have contributed to that outcome? From post hoc analysis of PREDIMED data, Estruch et al. [61] found that those who consumed as much EVOO and as many nuts as they wished (ad libitum) experienced a decrease in bodyweight and less gain in central adiposity, compared with the control diet (featuring no EVOO or nuts) and mention the gut microbiota as a potential mediator of this metabolic change. Was the participants' gut microbiota also a mediator of the beneficial effects on cognitive function [62–64], breast cancer [65], and metabolic syndrome [66] confirmed by further secondary outcome analysis of PREDIMED data? Quite possibly.

In a controlled-feeding, randomized crossover study of 18 healthy men and women (mean age \cong 53 years), Holscher et al. [67] found that those who consumed up to 42 g walnuts daily for 3 weeks had between 49% and 160% higher relative abundance of butyrate-producing *Clostridium* clusters XIVa and IV Firmicutes species such as *Faecalibacterium*, *Clostridium*, *Dialister*, and *Roseburia*, along with 16%–38% lower relative abundance of *Ruminococcus*, *Dorea*, *Oscillospira*, and *Bifidobacterium*. Walnut consumption was also seen to reduce the proinflammatory secondary bile acids deoxycholic and lithocholic acid, as well as LDL cholesterol. In a larger (n = 194, 134 women and 60 men) and longer randomized, controlled, prospective, crossover study, Bramberger et al. [68] put 96 people on a similar amount of walnuts as Holscher et al. (43 g/day) for 8 weeks, after which time participants moved on to a nut-free diet. Probiotic and butyric acid producing species were enhanced. Noteworthy

is that walnut consumption increased the abundance of *Ruminococcaceae* and *Bifidobacteria*, while *Blautia* and *Anaerostipes* (both *Clostridium* cluster XIVa species) were found in significantly lower numbers. The authors believe walnuts can help improve microbial diversity, with positive metabolic ramifications.

PREDIMED nuts also featured almonds and hazelnuts, and a number of studies have looked at both. With the MD being a system made up of a number of individual but interwoven components, it is difficult to unravel the contribution of every one. The systematic review by De Souza et al. [69] provides a thorough appraisal of nuts. Different factors including fatty acid profiles, vegetable protein, fiber, vitamin, and mineral content, as well as levels of phytosterols and phenolics, make each individual nut unique [70], as does the food processing.

Holscher et al. [71] provided 42 g/d of whole (unprocessed), whole roasted, roasted chopped almonds, or almond butter. They found that the relative abundance of *Roseburia*, *Clostridium*, and *Lachnospira* increased significantly, compared to those following a nut-free control diet period. Roasted chopped almonds seemed to have the strongest effect on relative abundance of the genus *Roseburia*, *Lachnospira*, and *Oscillospira*, while whole roasted almonds also increased the relative abundance of *Lachnospira* genus, with no differences for the almond butter group.

Complementing dietary diversity with fermented foods as sources of live microorganisms

Fermented foods, based on both dairy—yoghurt, kefir, cheese—and nondairy—sauerkraut, kimchi, kombucha—substrates are easily accessible dietary tools that can help modulate gut microbiota. A recent protocol supplemented 100 g a day of a probiotic yoghurt versus a high-strength probiotic supplement. The yoghurt contained just two strains of *Lactobacillus acidophilus* LA5 and *Bifidobacterium lactis* BB12 with 10^7 colony forming units (CFU)/g, and the supplement contained *Lactobacillus casei* 3×10^3 , *L. acidophilus* 3×10^7 , *Lactobacillus rhamnosus* 7×10^9 , *Lactobacillus bulgaricus* 5×10^8 , *Bifidobacterium breve* 2×10^{10} , *Bifidobacterium longum* 1×10^9 , and *Streptococcus thermophilus* 3×10^8 CFU/g, with 100 mg of fructo-oligosaccharide and lactose as carrier substances. The control group was given a conventional yoghurt containing the starter cultures of *S. thermophilus* and *L. bulgaricus* and experienced no statistically significant improvement in mental health markers, which included depression, anxiety, and stress based on validated scales [72]. The fact the study reported similar effectiveness of a supplement and a whole-food intervention is encouraging. Yoghurt is a low cost and versatile food that can be served or blended with a variety of fresh foods and spices,

e.g., fruit, cinnamon, ginger, thereby minimizing expense, while improving patient compliance.

In another randomized controlled trial, researchers at the University of Connecticut [73] found that premenopausal women who ate just 339 g of yoghurt for 9 weeks experienced a reduction in biomarkers of chronic inflammation and endotoxin exposure (including LPS, LPS-binding protein, IgM endotoxin-core antibody (IgM EndoCAB), and zonulin). The yoghurt used in the intervention group happened to be low fat. Based on the natural low fat content of yoghurt, it is questionable whether comparable results would have been achieved using full-fat yoghurt instead.

While the endpoints measured were different, a 5-year prospective study of 4545 elderly individuals (55–80 years of age), at high cardiovascular risk, evaluated the association between yoghurt consumption and the reversion of abdominal obesity status. Whole-fat yoghurt had a more beneficial effect than low fat yoghurt varieties [74]. Additional health benefits of regular yoghurt consumption include the support of effective weight management [75], improved lactose digestion [76], and lower risk of developing T2D [77].

It has been difficult to distinguish between yoghurt benefits derived from the nutrients contained in the food matrix, e.g., calcium, vitamin B₁₂, etc., and those associated

with the fermenting microorganisms, making it more of a challenge attributing separate effects to fermented foods alone, than as part of a whole dietary pattern.

Final considerations

Diversity of fresh produce is a key contributor to a healthy microbial population, a state known as *eubiosis*, which contrasts with the previously discussed perturbed state of dysbiosis. The authors are both practitioners and clinical researchers, involved in the design and implementation of clinical trials, assessing the impact of foods on the microbiome and on mental health markers. Having carried out extensive, ongoing review of the literature, they propose that polyphenol-rich vegetables, legumes, fruit, herbs, spices, and olive oil, plus the fermented foods typically featured in the Mediterranean dietary pattern, plus the tendency to include fewer ultraprocessed food items than standard British or American diets are the two most significant factors contributing to the characteristics of a eubiotic or healthy gut ecosystem, such as that described in studies delving into the microbial composition and metabolites in the gut of Mediterranean populations. This is illustrated in Fig. 43.3.

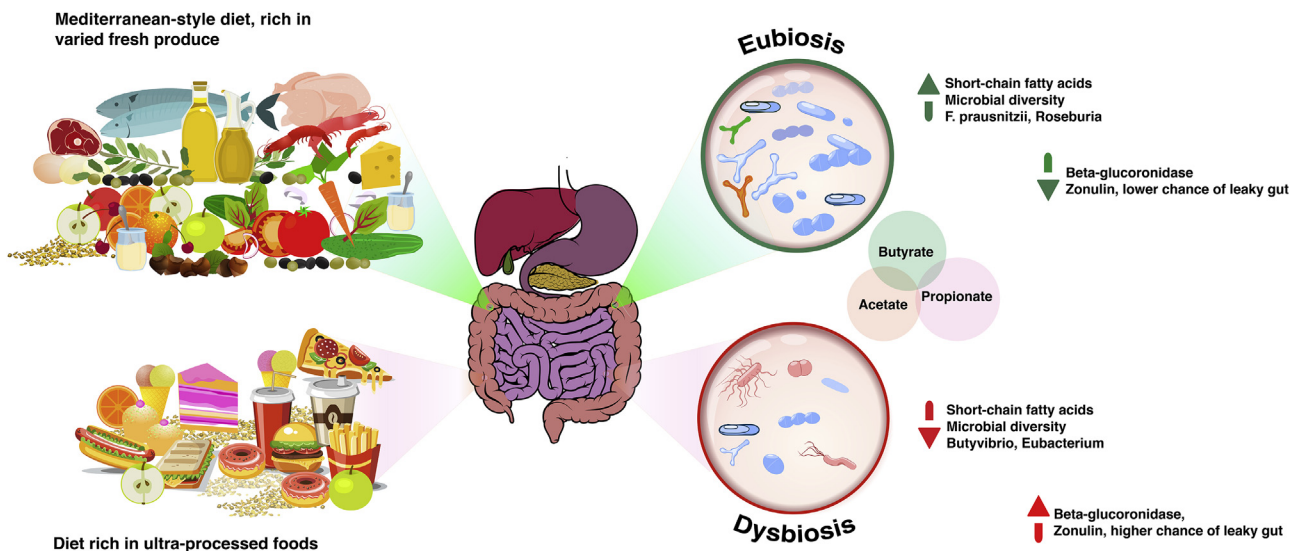


FIGURE 43.3 Achieving and maintaining a healthy gut microbial ecosystem with a Mediterranean-type dietary pattern. Dietary patterns that are rich in fresh produce, including a variety of brightly colored vegetables and fruits, olive oil, nuts, and seeds, e.g., a Mediterranean-style diet, are seen to promote eubiosis, contributing to higher levels of all three short-chain fatty acids and to a wider microbial diversity. Other characteristics of a eubiotic gut ecosystem include lower levels of beta-glucuronidase, documented to help with normal elimination of toxicants, and lower zonulin levels, seen as an indication of reduced susceptibility of damage to the intestinal barrier, i.e., less “leaky gut”. On the other hand, dietary patterns rich in ultraprocessed foods and particularly those rich in refined carbohydrates combined with high fat levels are seen to promote gut dysbiosis. Lower microbial diversity and lower levels of short-chain fatty acid levels are seen in patients whose diets consist of mostly of ultraprocessed foods. Other markers are also affected. Beta-glucuronidase may be higher, which could pose issues with toxicant elimination via reduced activity of phase II detoxification pathways. There is also a higher susceptibility for barrier tissue damage. Higher zonulin levels in stool would give practitioners an indication that this is the case. A disrupted intestinal barrier tends to be correlated with a number of negative health outcomes. Adapted from Toribio–Mateas, M. *Harnessing the power of microbiome assessment tools as part of neuroprotective nutrition and lifestyle medicine interventions*. *Microorganisms* 2018;6:35.

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