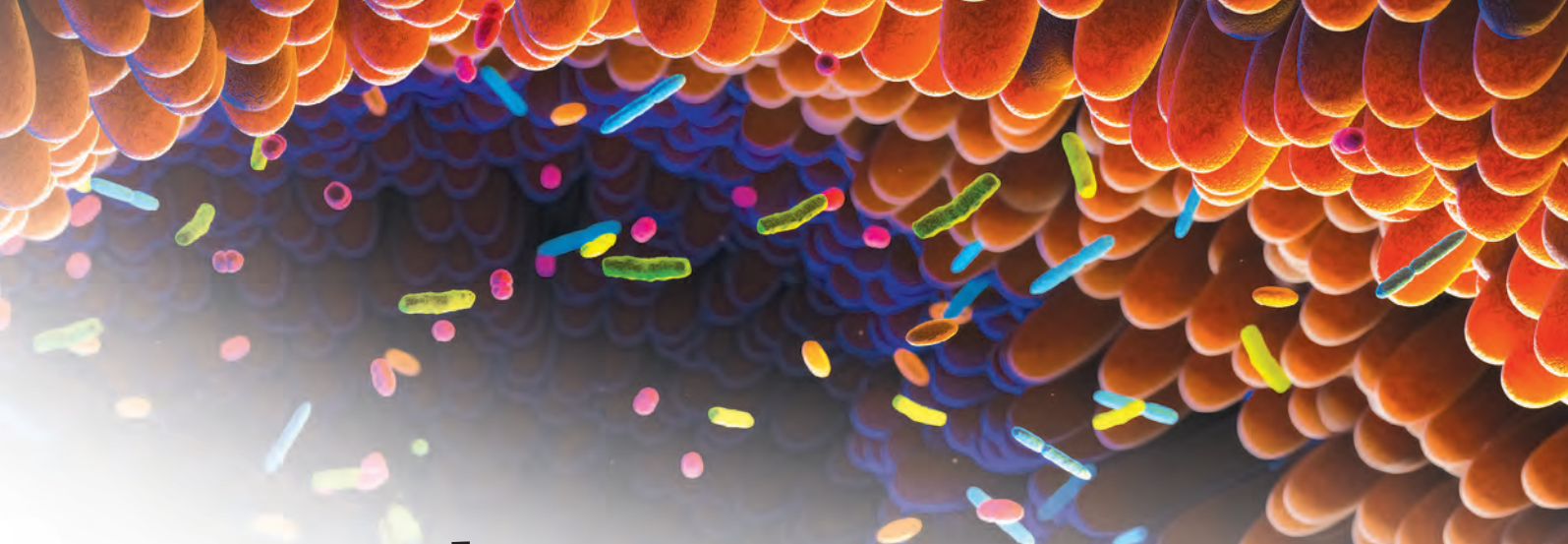

Microbiome

The importance of maintaining a healthy gut through the lifespan

Antonella Rossino, Registered Dietitian

Our gut plays host to an intricately balanced population of microbes that have an essential role in our health throughout our lifetimes. Disturbances, or dysbiosis, to this homeostatically controlled environment has been implicated in the pathogenesis of age-related chronic diseases and a significant number of poor health outcomes, including obesity, cardiovascular diseases and neurodegenerative diseases. The population of the microbiome as we advance through life may be a predictor of survival in old age, and manipulation of the population may provide areas for therapeutic intervention to support healthy ageing and longevity. In this article, the evolution of the microbiome from birth to elderly age, and how we can support and enrich the beneficial populations for optimum health, will be explored.

Early life establishment

The gut microbiome – theorised to begin colonisation as early as in the foetal stage, through the presence of bacteria in the placenta[1] and the amniotic fluid[2] – is made up of trillions of microorganisms, mainly bacteria, as well as viruses, fungi and archaea. Ninety-eight per cent of all the microrganisms present are made up of the 4 bacterial phyla: firmicutes, bacteriodes, proteobacteria and actinobacteria. In healthy individuals these organisms, which mainly reside in the small and large intestines but also in small numbers throughout other areas of the body including the oral cavity and skin, are involved in a symbiotic relationship for the benefit of host health.[3] Amongst its important roles, the gut microbiome supports both the digestion and absorption of the food we consume, metabolises fibre into short chain fatty acids (SCFAs), maintains intestinal integrity, produces vitamins and hormones, and regulates host immunity.[4]

The most critical period of change and susceptibility for manipulation of our gut microbiome occurs in infancy and old age, and although our DNA primarily dictates our microbial population in the first instance, the establishment and development of the microbiome is hugely influenced by many different factors, particularly in the first 3 years of life. The maternal microbiota, mode of delivery, infant feeding, medication use, and even geographical location, all have a significant impact on the colonisation of the microbiota in the early stages.[5]

The way in which we birth is one of the earliest interventions that contribute to the colonisation of the gut microbiota. Vaginal delivery exposes baby to perianal and vaginal microbes,[5] as well as environmental factors and skin microbes. Babies delivered by caesarean section in contrast, are limited to the exposure of environmental and skin microbes only.[5] As a result, babies born via vaginal delivery methods have an increased abundance of bacteroides and lactobacilli, which is not replicated in their caesarean born counterparts. Infants born by caesarean have an increased likelihood of colonial dominance with *Clostridium (C.) difficile, C. perfringens*, and *Escherichia (E.) coli*.[6] It is important to note, however, that birth via caesarean section also coincidentally leads to increased duration of hospital stays and increased use of antibiotics, factors which in themselves have the ability to manipulate the establishment of the microbial populations in the gut.[7]

Following birth, the neonatal diet can also be attributed to the on-going development of the gut microbiota. The stimulation of probiotic bacteria, such as bifidobacterium and lactobacillus,[8] is fed by the rich source of prebiotic human milk oligosaccharides (HMOs) in human breast milk,[9] and found to be in reduced levels in babies fed formula milk.[10] By the time weaning onto solid food occurs, the microbial population of the gut becomes increasingly unique to the individual, although the differences previously associated with breastfed and formula fed babies becomes less apparent. From this point onwards, diet becomes the contributing factor for the continued maintenance of a stable gut microbial population throughout life.[11]

As outlined, the first 3 years of a child's life are critical to the establishment of the gut microbiome and provide an opportunity to maximise development and reduce chances of future health complications. For instance, if we focus on the topic of allergy in children, a condition which has been rising significantly in recent years. Western society has particularly high levels of allergy,[12] with the UK having some of the highest rates in the world.[13] This may be attributable in part to a diet which is dominant in meat-based products, high in fat, and low fibre intakes. The digestion of fibre produces important metabolites, such as butyrate from the digestion of SCFAs. These imperative metabolites may signal for the development, maturation and integrity of the intestinal epithelial barrier and associated mesenteric lymph nodes, lymphoid tissue (Peyers patches) and lymphoid follicles.[14] Dysbiosis can result in the entry of antigens in the bloodstream and the abnormal stimulation of the immune system leading to an allergenic profile.[15, 16] From the evidence, it may be sensible to infer that a more plant-based diet, which is naturally high in fibre, right from weaning on to solid foods, may be one of the controllable factors that could contribute to reducing the development of allergy.

From childhood and beyond

From ages 3-5, the composition and diversity of the gut population resemble that of an adult and remains relatively stable.[17] As we enter adulthood, the gut microbiota is dominated by the *firmicutes* and *bacteroidetes* phyla and smaller numbers of *actinobacteria, proteobacteria* and *verrucomicrobia*[18] and as we progress through our life, natural fluctuations in the population of the gut microbiota occur.[7] There are instances, however, where this natural stability is threatened. One such example is antibiotic use. Whilst we can all agree antibiotics have been essential for having improved the morbidity and mortality outcome of many bacterial illnesses, their use has none-the-less come at a detriment to our gut health.[19] A significant body of evidence shows that dysbiosis of the gut microbial population from use of antibiotics, whether that be in infancy or in later life, can be linked to the development of obesity,[20] diabetes[21] and asthma.[22] These conditions, on the whole, may possibly be prevented from occurring if we can identify some of the controllable factors involved in their development. This may be identifying and manipulating the contributing microbial component alongside dietary specific causes and interventions. There is scope for exploring the use of alternatives to antibiotics and probiotics as a therapeutic intervention alongside antibiotic use.

Maintaining a healthy microbiome into old age

The gut microbiome has been implicated in age-related health decline.[23] Ageing is a complex, physiological process, and what is determined as healthy ageing is not solely influenced by one factor, but rather due to a combination of genetics and lifelong environmental and lifestyle factors.[24] Research has therefore focused on trying to establish causal links between the gut microbiome and the ageing host.

Although it is overall unclear whether changes in the population of the gut microbiota in host ageing are a cause or a consequence, it is certainly identifiable that elderly people have a different microbial profile, with less diversity, compared with healthy adults. This difference can be linked with occurrences of advancing age, such as changes in dietary and lifestyle practices, reduced mobility, weakened immune strength, reduced intestinal functionality and the increased incidence of hospitalisation and medication.[25] It does appear that the beneficial microbes, including bacteroides, bifidobacteria and lactobacilli, are found to be reduced as age advances, whilst the levels of opportunistic microbes, such as enterobacteria, *C. perfringens* and *C. difficile,* are in contrast increased.[25] This shift in microbial population also leads to a reduction in production of SFCAs, which have an essential role in immune and inflammatory responses.[26]

From middle-age, studies have shown that the gut microbiome becomes increasingly unique to individuals with advancing age. As age increases past 80 years, healthy individuals showed a continued shift towards a unique microbial population, which is absent in less healthy individuals.[27] Exploring the population composition further shows that retaining a high number of bacteroides alongside reduced gut uniqueness can predict decreased survival.[27] The study by Wilmanski *et al.* (2021) showed that beneficial blood metabolites produced by gut bacteria were raised and levels of low-density lipoprotein cholesterol were reduced in the individuals with a more diverse gut microbiome.[27]

Figure 1 details age-related changes and other factors that could affect our gut microbiome.

How can we help our gut for a healthier life?

Probiotics and therapeutic interventions to optimise gut microbiota

Probiotics are increasingly seen as a way of restoring or manipulating the gut bacteria for benefit. Probiotics are increasingly seen as a way of restoring or manipulating the gut bacteria for benefit, including following antibiotic treatment. Unfortunately, whilst highly beneficial, the scope for use of probiotics may be at points limited. Studies have undeniably shown particular strains, such as lactobacilli and bifidobacteria, are valuable in modifying gut bacteria; however, there is a large degree of inconclusiveness as to how they may affect other health outcomes associated with ageing.[28, 29] Therefore, other avenues of therapeutic intervention for modifying gut microbial populations have been worth exploring. Faecal microbiota transplant, for instance, has been used successfully to restore the gut microbial population in patients with *C.difficile*.[30] Because of its low cost and efficacy, this option provides huge potential for further exploration. With further research, it is hoped that the therapeutic applications can be optimised in order to improve health.

Dietary interventions to maintain a healthy gut microbiome

Whilst some aspects which affect our gut microbiome are beyond our control, there are many modifiable and lifestyle factors that we can focus on to help maintain a healthy gut microbiome throughout our lives. The Western diet, with its propensity

for high intakes of meat, high fat and processed foods and low intake of fibre, has long been linked to an array of poor health outcomes, as well as negatively affecting the gut microbiome.[31] Despite this, studies have shown that changing and maintaining our diet for the better can change the population of the gut microbiome within just a few short days.[32] Current guidance recommends that we aim for an intake of 30 or more plant foods per week. This includes, fruits, vegetables, legumes, nuts, seeds and wholegrains, and following a plant-focused diet (e.g. Mediterranean diet) is associated with beneficial microbiome related profiles.[33] Reducing our reliance on artificial sweeteners and preservatives, which have been shown in animal studies to negatively affect our gut bacteria, may also lead to more positive health outcomes.[34, 35]

Conclusion

The vast array of microbes which colonise our gut microbiome throughout our life, have an essential role in not only impacting disease development, but also how well we age and have been linked to human longevity. Whilst it can be difficult to establish causality, research shows that critical periods in childhood and in elderly age can define our future health, and throughout life there are opportunities for manipulating our gut bacteria for benefit. Although some research into gut microbial ageing remains in its infancy, we can maximise the beneficial populations by concentrating on a plant-based diet with its high fibre focus, reducing our intake of processed food, artificial sweeteners and additives, and exploring the inclusion of probiotics in the diet. The future offers an exciting avenue for continued development and for the potential of designing optimum diets personalised for our own unique gut bacteria to yield better health and ageing outcomes.

Figure 1: Human gut microbial ecosystem – age-related changes & potential factors that could affect the microbiota composition[7]

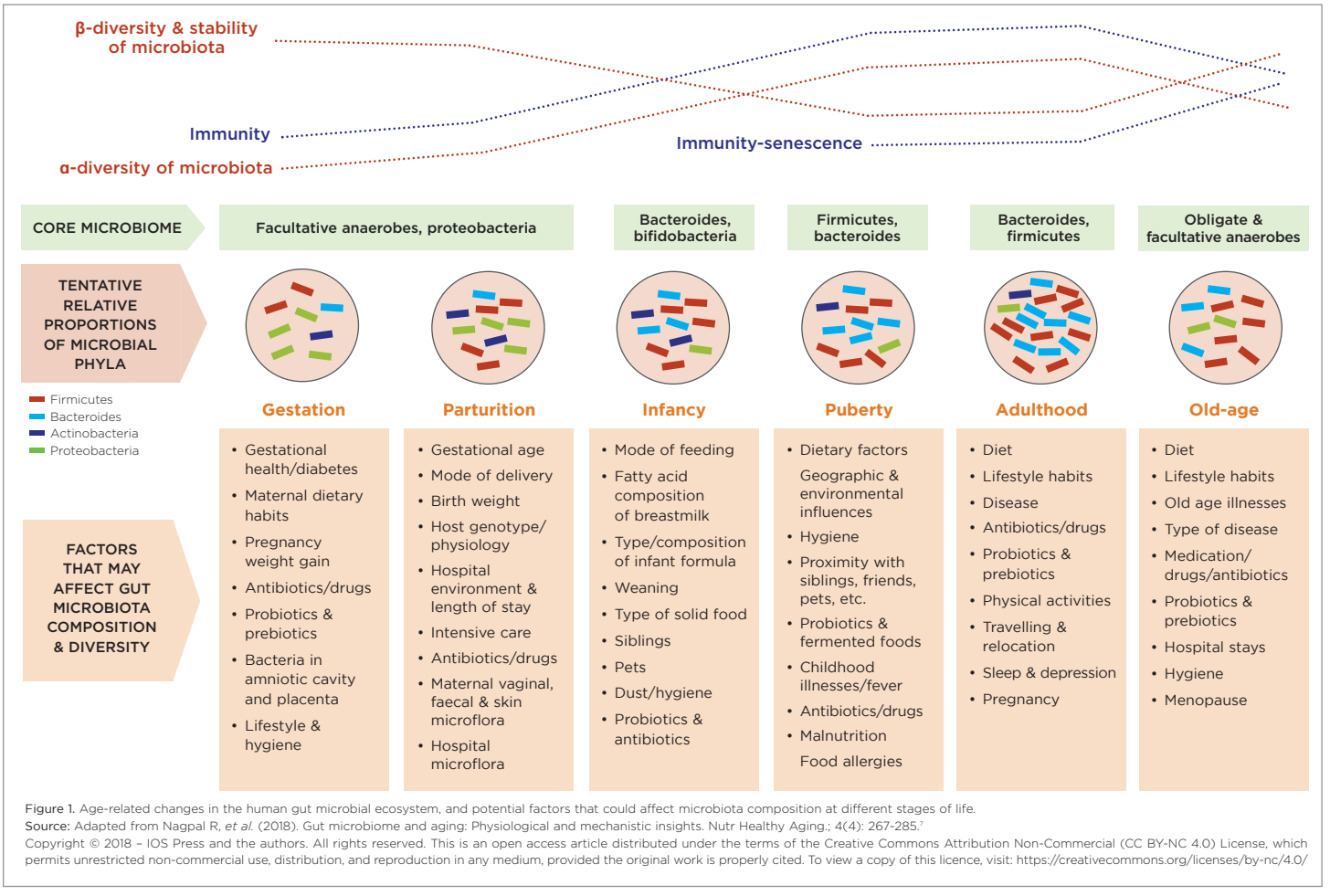

Figure 1. Age-related changes in the human gut microbial ecosystem, and potential factors that could affect microbiota composition at different stages of life.
Source: Adapted from Nagpal R, *et al.* (2018). Gut microbiome and aging: Physiological and mechanistic insights. Nutr Healthy Aging.; 4(4): 267-285.[7]

References: **1.** Aagaard K, *et al.* (2014) The placenta harbors a unique microbiome. Sci Transl Med.; 6(237): 237ra65. **2.** DiGiulio DB, *et al.* (2008). Microbial prevalence, diversity and abundance in amniotic fluid during preterm labor: a molecular and culture-based investigation. PLoS One.; 3(8): e3056. **3.** Ragonnaud E, Biragyn A. (2021). Gut microbiota as the key controllers of "healthy" aging of elderly people. Immun Ageing.; 18(1): 2. **4.** Gill SR, *et al.* (2006). Metagenomic analysis of the human distal gut microbiome. Science.; 312(5778): 1355-1359. **5.** Molloy J, *et al.* (2013) The potential link between gut microbiota and IgE-mediated food allergy in early life. Int J Environ Res Public Health.; 10(12): 7235-7256 **6.** Bokulich NA, *et al.* (2016). Antibiotics, birth mode, and diet shape microbiome maturation during early life. Sci Transl Med.; 8(343): 343ra82. **7.** Nagpal R, *et al.* (2018). Gut microbiome and aging: Physiological and mechanistic insights. Nutr Healthy Aging.; 4(4): 267-285. **8.** Jost T, *et al.* (2015) Impact of human milk bacteria and oligosaccharides on neonatal gut microbiota establishment and gut health. Nutr Rev.; 73(7): 426-437. **9.** Yassour M, *et al.* (2016) Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability. Sci Transl Med.; 8(343): 343ra81 **10.** Dethlefsen L, Relman DA. (2011). Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. Proc Natl Acad Sci USA.; 108 (Suppl 1): 4554-4561. **11.** David LA, *et al.* (2014). Diet rapidly and reproducibly alters the human gut microbiome. Nature.; 505(7484): 559-563. **12.** Tan J, *et al.* (2016) Dietary fiber and bacterial SCFA enhance oral tolerance and protect against food allergy through diverse cellular pathways. Cell Rep.; 15(12): 2809-2824. **13.** Levy ML, *et al.* (2004) Sheikh A. Inadequacies in UK primary care allergy services: national survey of current provisions and perceptions of need. Clin Exp Allergy.; 34(4): 518-519. **14.** Akagawa S, Kaneko K (2022). Gut microbiota and allergic diseases in children. Allergol Int.; 71(3): 301-309. **15.** Iweala OI, Nagler CR. (2019) The microbiome and food allergy. Annu Rev Immunol.; 37: 377-403. **16.** Maynard CL, *et al.* (2012). Reciprocal interactions of the intestinal microbiota and immune system. Nature.; 489(7415): 231-241. **17.** Yatsunenko T, *et al.* (2012). Human gut microbiome viewed across age and geography. Nature.; 486(7402): 222-227. **18.** Eckburg PB, *et al.* (2005). Diversity of the human intestinal microbial flora. Science.; 308(5728): 1635-1638. **19.** Patangia DV, *et al.* (2022). Impact of antibiotics on the human microbiome and consequences for host health. Microbiologyopen.; 11(1): e1260. **20.** Riley LW, Raphael E, Faerstein E. (2013). Obesity in the United States - dysbiosis from exposure to low-dose antibiotics? Front Public Health.; 1: 69. **21.** Boursi B, *et al.* (2015). The effect of past antibiotic exposure on diabetes risk. Eur J Endocrinol.; 172(6): 639-648. **22.** Arrieta MC, *et al.* CHILD Study Investigators; Mohn WW, Turvey SE, Finlay BB. (2015). Early infancy microbial and metabolic alterations affect risk of childhood asthma. Sci Transl Med.; 7(307): 307ra152. **23.** Ghosh TS, Shanahan F, O'Toole PW. (2022). The gut microbiome as a modulator of healthy ageing. Nat Rev Gastroenterol Hepatol.; 19(9): 565-584. **24.** Kenyon CJ (2010). The genetics of aging. Nature; 464(7288): 504-512. **25.** Odamaki T, *et al.* (2016). Age-related changes in gut microbiota composition from newborn to centenarian: A cross-sectional study. BMC Microbiol.; 16(1): 90. **26.** Ale EC, Binetti AG. (2021). Role of Probiotics, Prebiotics, and Synbiotics in the Elderly: Insights Into Their Applications. Front Microbiol.; 12: 631254. **27.** Wilmanski, T, *et al.* (2021). Gut microbiome pattern reflects healthy ageing and predicts survival in humans. Nat Metab.; 3(2): 274-286. **28.** Bedani R, Isay Saad SM, Sivieri K. (2016). Potential benefits of probiotics, prebiotics, and synbiotics on the intestinal microbiota of the elderly, in Probiotics, prebiotics, Synbiotics: Bioactive foods in health. eds. Watson RR, Preedy VR. London, UK: Academic Press, Elsevier.; 525-538. **29.** Hutchinson AN, *et al.* (2021). The Effect of Probiotics on Health Outcomes in the Elderly: A Systematic Review of Randomized, Placebo-Controlled Studies. Microorganisms.; 9(6): 1344. **30.** Weingarden AR, *et al.* (2014). Microbiota transplantation restores normal fecal bile acid composition in recurrent Clostridium difficile infection. Am J Physiol Gastrointest Liver Physiol.; 306(4): G310-319. **31.** Shi Z (2019). Gut Microbiota: An Important Link between Western Diet and Chronic Diseases. Nutrients; 11(10) :2287. **32.** O'Keefe SJD, *et al.* (2015). Fat, fibre and cancer risk in African Americans and rural Africans. Nat Commun.; 6: 6342. **33.** Tosti V, Bertozzi B, Fontana L. (2018). Health Benefits of the Mediterranean Diet: Metabolic and Molecular Mechanisms. J Gerontal A Biol Sci Med Sci.; 73: 318-326. **34.** Nettleton JE, Reimer RA, Shearer J. (2016). Reshaping the gut microbiota: Impact of low calorie sweeteners and the link to insulin resistance? Physiol Behav.; 164(Pt B): 488-493. **35.** Chassaing B, *et al.* (2015). Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. Nature.; 519(7541): 92-96.