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The Gut Microbiome, Aging and Longevity- An Overview

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ABSTRACT

The gut microbiome is a contributory factor in ageing-related health loss and in several non-communicable diseases in all age groups. Some age-linked and disease-linked compositional and functional changes overlap, while others are distinct. The gut microbiota undergoes extensive changes across the lifespan, and age-related processes may influence the gut microbiota and its related metabolic alterations. The aim of this systematic review was to summarize the current literature on aging-associated alterations in diversity, composition, and functional features of the gut microbiota. Longevity is one of the most complex phenotypes, and its genetic basis remains unclear. This study aimed to explore the genetic correlation and potential causal association between gut microbiota and longevity. Human longevity has a strong familial and genetic component. Dynamic characteristics of the gut microbiome during aging associated with longevity, neural, and immune function remained unknown. Here, we aim to reveal the synergistic changes in gut microbiome associated with decline in neural and immune system with aging and further obtain insights into the establishment of microbiome homeostasis that can benefit human longevity. In this paper we will discuss The Gut Microbiome, Aging and Longevity- an Overview.

KEYWORDS: *Gut Microbiome, Aging, Longevity, Human longevity, gut microbiota, Healthy Aging, Healthy Microbiome, Cognitive Health*

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INTRODUCTION

Ageing is a natural process that practically all biological creatures go through. Ageing is accompanied by progressive organismal degeneration and a loss in cellular function, exposing individuals to a variety of pathological illnesses. Humans are more likely to develop cardiovascular and neurological disorders, cancer, and diabetes, among many other chronic diseases, as they age. [1]

Everyone ages, yet the negative consequences of ageing on physical and cognitive performance are not felt universally. Many people exhibit delayed age-related deterioration, also known as 'healthy' ageing. Genetic, environmental, and lifestyle variables are all determinants of good ageing, with the latter providing a possibility for intervention. The microbiome processes environmental cues, influences host immunological, metabolic, and neurological function, and influences illness risk, including age-related disorders. The microbiome, on the other hand, has a reciprocal relationship with age: it changes as the host ages and is altered in age-related disease, but it also affects the host's age-related impairment.

Ageing is the process of ageing older, which is genetically determined and influenced by the environment. Changes in the dynamics of biological, environmental, behavioural, and social processes are all involved. Genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis are primary cellular and molecular hallmarks of ageing, which lead to compensatory mechanisms such as deregulated nutrient sensing, mitochondrial dysfunction, and cellular senescence; ultimately, these lead to stem cell exhaustion and altered intercellular communication, which are responsible for the functional decline associated with ageing. The rapid advancement of next-generation sequencing technologies has the potential to shed light on the molecular and genetic pathways underlying ageing and age-related disorders. [2]

In order to gain a better understanding of the relationship between the gut microbiota and a long-living host, we present for the first time a phylogenetic microbiota analysis of semi-supercentenarians (105-109 years old) in comparison to adults, the elderly, and centenarians, thereby reconstructing the longest available human microbiota trajectory along ageing. We found a core microbiota of highly prevalent, symbiotic bacterial taxa (mainly from the dominating Ruminococcaceae, Lachnospiraceae, and Bacteroidaceae families), with cumulative abundance decreasing with age. Ageing is marked by an increase in the abundance of subdominant species as well as a reorganisation of their co-occurrence network. These characteristics are preserved in longevity and extreme longevity, but peculiarities emerged, particularly in semi-supercentenarians, describing changes that, while accommodating opportunistic and allochthonous bacteria, may possibly support health maintenance during ageing, such as an enrichment and/or higher prevalence of healthassociated groups (e.g., Akkermansia, Bifidobacterium, and Christensenellaceae). [3]

Beginning in mid-to-late adulthood, individuals' gut microbiomes grew progressively distinct (i.e., increasingly diverged from others), which correlated with a continuous drop in the number of key bacterial species (e.g., Bacteroides) that are shared throughout people.

Surprisingly, while microbiomes were increasingly unique to each individual with healthy ageing, the metabolic tasks performed by the microbiomes shared similar characteristics.

This gut uniqueness signal was highly linked with many microbially-derived compounds in blood plasma, including one -- tryptophan-derived indole -- that has previously been proven to enhance mouse lifetime.

Another metabolite, phenylacetylglutamine, had the strongest connection with uniqueness, and previous research has revealed that this metabolite is actually considerably higher in the blood of centenarians.

Longevity is one of the most complex phenotypes investigated to date, with numerous complex elements influencing ageing and life expectancy, such as income, diet, education, and health services. Furthermore, a longer life does not necessarily imply a longer healthspan, with the most frequent complicated diseases increasing with age. Previous research has revealed that genetic and environmental factors influence longevity and healthy ageing. The heritability of adult death age is roughly 25%. Non-genetic factors that contribute to lifespan include social position, non-smoking, and food habits. [4]

The genome-wide association study (GWAS) has been widely utilised to investigate possible genetic variations for a wide range of complex traits and disorders, including longevity and gut microbiota. Genetic correlation is a key population metric for describing the genetic association of various phenotypes. Its application could lead to a better understanding of hereditary and pathogenesis pathways in complicated disorders. Based on GWAS summary data, linkage disequilibrium score (LDSC) regression is a strong technique for estimating genetic connections across human complex characteristics. The use of summary statistical data rather than individual-level genotyping data is a significant advantage of LDSC for large-scale analyses, making data analysis more convenient, as most big GWAS analyses publish summary statistical results. It has been widely utilised for determining the common genetic architecture of complex traits, such as evaluating the heritability of immune-related diseases and various psychiatric disorders and testing for genetic association. [5]

With a widespread decline in health, it is unclear what "healthy ageing" truly entails. There is no agreed-upon concept of healthy ageing vs ill ageing. Heterogeneity is a feature of ageing. As people age, they become more dissimilar to one another. Even tissues within the same body age at different rates. Ageing can be researched from several viewpoints, including "normal" (average or typical) ageing, pathological ageing (related with specific diseases or other markers of accelerated ageing), and effective ageing.

The current review concentrated on healthy and successful ageing, ignoring disease-related pathological ageing. Individuals that live extremely long lives, such as centenarians, are examples of extraordinarily successful ageing. They have escaped or survived the majority of the diseases that cause morbidity and mortality in most other older persons; nonetheless, they may still exhibit certain ageing symptoms. These elderly people can provide valuable insights on the most perfect of ageing processes. Inflammation is still present in long-lived people (nonagenarians and centenarians), but less so than “normal” older adults, and their pro-inflammatory status is balanced by concomitant anti-inflammatory responses. [6]

Changes in the Gut Microbiota Associated with Longevity or Healthy Aging:

One potentially fruitful strategy to investigating the functions of the gut microbiota in human ageing is to

collect age-related changes in the gut microbiota and see if these changes have any biological significance. Cross-sectional investigations of faecal samples from people of various ages show that the makeup and diversity of the gut microbiota change with age, which is consistent with the findings of longitudinal studies.

In general, as people get older, their gut microbiota grows more diverse and variable. For example, the three bacterial families listed in the preceding section become less abundant in older age groups, whereas certain health-associated species become more abundant in older age groups, including centenarians and semi-supercentenarians. [7]

Animal Models of Gut Microbiota in Longevity and Healthy Aging:

Nutrient Signaling Pathways

Nutrition is the most important component in shaping the host's gut microbiota. It also has an impact on the host's epigenome; for example, as dietary methyl donors, folate and choline can influence DNA methylation.

Furthermore, nutrition is an important environmental element that interacts with host genes, particularly those involved in nutrient signalling pathways. Nutrition is thus a common element that can connect the gut microbiome to the host genome.

A moderate reduction in food intake, known as dietary or caloric restriction (CR), improves both health and lifespan. It is a widely conserved intervention that engages biological mechanisms that have been conserved throughout evolution, from yeast to primates. However, much remains to be discovered. Because alterations to gustatory or olfactory neurons, or even treatment of animals with diet-derived odours, can modulate longevity in Caenorhabditis elegans and Drosophila melanogaster, nutrient availability may not be the only input that might affect the pathways that trigger the CR response. [8]

The immune system is essential for host defence against harmful organisms and illness prevention. Immunosenescence, or age-related immune system remodelling, results in a decrease in immune system protective components and chronic, low-grade inflammation, which is referred to as "inflammaging."

Aged individuals are more susceptible to infectious diseases and have a higher risk of developing the noncommunicable diseases described above; therefore, immunosenescence is a major contributor to the declining health of the aging population. The gut microbiome is considered to be an important factor contributing to host health, as it plays a significant role in immune system function. Arguably, two of the most influential lifestyle behaviors that promote health are consuming a nutritious, well-balanced diet and partaking in regular physical activity. Diet and exercise are well-known to modulate immune function and inflammation; however, less understood is the interaction between diet, exercise, and the gut microbiome with aging.

The Aging Microbiome:

Understanding the changes to the microbiome that occur as part of the ageing process is critical to understanding how external influences such as nutrition and exercise may influence the gut microbiota. The gastrointestinal system begins to colonise with bacteria from birth, forming the gut microbiome. The diversity of gut microbes grows with age and exposure to changing surroundings, such as stress, food, and exercise. This highlights the fragility of microbiota population variations. Birth, adolescence, and old life are three critical phases in the formation of the gut microbiota. [9]

A Healthy Microbiome Contributes to Longevity:

Given that your gut microorganisms influence so many critical physiological functions, including immune response and cognitive ability, it's only natural that they influence your ageing process and contribute to longevity and wellbeing.

Immune System Support

A diversified and balanced microbiome is essential for a healthy immune system. A strong immune response assists your body in fighting infections and disorders, improving general health and potentially prolonging your life.

Inflammation Regulation

A healthy microbiome helps manage low-grade inflammation, limiting excessive immune responses and lowering the risk of chronic inflammatory disorders that restrict nutrient absorption.

Metabolic Health and Weight Regulation

Your gut microorganisms govern your natural metabolism and energy balance, allowing you to maintain a healthy weight and prevent metabolic illnesses like obesity and type 2 diabetes, which can shorten your life.

Nutrient Absorption and Synthesis

Your microbiota aids in the digestion of complex nutrients and the production of specific vitamins, resulting in proper nutrient absorption, which is critical for your general health.

Protection Against Pathogens

A varied microbiome protects against pathogen overgrowth by competing for resources and creating

antimicrobial chemicals. This protection helps to maintain the integrity of your intestinal barrier and minimises the danger of infections that can shorten your life.

Cognitive Health

Keep in mind the gut-brain axis. This interaction between your gut and brain has an impact on your cognitive health and brain function. It lowers the risk of age-related diseases and neurological issues, allowing people to live longer and healthier lives.

Heart Health

A healthy microbiota may help to keep your blood vessels, cholesterol levels, and blood pressure in check, lowering your risk of heart disease and encouraging longevity. [10]

Review of Literature:

The study of the extreme limits of human lifespan may lead to a greater understanding of how humans can avoid, postpone, or endure the most common age-related causes of illness, a trait shared by the elderly. Longevity is a complex attribute in which genetics, environment, and stochasticity all work together to determine the likelihood of living to be 100 years old or older. The gut microbiome has been hypothesised as a possible determinant of healthy ageing due to its impact on human metabolism and immunology. Indeed, maintaining host-microbe homeostasis helps prevent ageing, intestinal permeability, and bone and cognitive health loss. C.R. Villa (2015). [11]

Certain compositional and diversity changes are related with biological or functional age, regardless of chronological age. Various markers of frailty have been employed as biological age indicators, and gut microbiota composition is related to biological age. Furthermore, gut microbial diversity is inversely related to biological age but not chronological age. Furthermore, with increasing biological age, a co-abundance module composed of Ruminococcus, Coprobacillus, and Eggerthella species becomes abundant (Maffei et al.). The first two genera in this module are Firmicutes, while the last one is Actinobacteria. According to one interpretation of these findings, as biological age grows, the total richness of gut microbiota diminishes, but specific microbial taxa linked with unhealthy ageing develop. Thus, what happens in the gut microbiota as biological age advances can be considerably different from what happens as chronological age advances, emphasising the necessity of employing a biological or functional measure in ageing investigations. [12]

The Gut Microbiome's Role in Health and Disease: To generate extremely sophisticated immune responses, the immune system has barrier, recognition, elimination, and memory capabilities, as well as diverse cell types and chemical mediators. The immune system can then defend the host against pathogenic organisms and balance the pro- and anti-inflammatory states. Individuals with compromised immune systems are more vulnerable to infections, persistent, low-grade inflammation, and the development of noncommunicable diseases. The human gastrointestinal (GI) tract is important in the immune response because it contains a complex and diverse community of bacteria, known as the gut microbiota, that can influence the host's health and disease. The gut microbiome is an important role in establishing the host immune response, and imbalance of the gut microbiota may be responsible for some chronic immunological-related illnesses. Honda, K. (2012). [13]

The gut microbiota is a varied set of bacteria found in the GI tract, and its genes are referred to as the microbiome. Each person has a distinct microbiota composition that is impacted by biological variables such as genetics as well as lifestyle factors such as nutrition exercise, sleep deprivation medicines, and mental health (Barandouzi et al., 2020). [14]

Objectives:

- ‘‘Longevity adaptation’’ seems to involve enrichment in health-associated gut bacteria.
- A core microbiota accompanies human life, decreasing in abundance along with aging.
- Aging is unavoidable in the human life cycle, characterized by progressive physiological decline, leading to increased frailty, disease, and decreased longevity.

Research Methodology:

This study's overall design was exploratory. The produced paper is a nature descriptive research. Secondary data and information were thoroughly analysed in order to prepare the report. Secondary data was gathered from various scholars' and researchers' published books, articles published in various journals, periodicals, conference papers, working papers, and websites.

Result and Discussion:

Genetic Correlation Between Gut Microbiota and Longevity:

LDSC detected 4 candidate genetic correlation between gut microbiota and longevity-related traits (Table 1), such as Veillonella (genetic correlation = 0.5578, P = 4.67 × 10− 2) and Roseburia (genetic correlation = 0.4491, P = 2.67 × 10− 2) for longevity, Collinsella (genetic correlation = 0.3144, P = 4.07 × 10− 2) for parental lifespan, and Sporobacter (genetic correlation = 0.2092, P = 3.53 × 10− 2) for health span. [15]

Table 1: Four candidate genetic correlations between gut microbiota and longevity-related traits

Gut microbiota	Phenotype	Genetic correlation	*P*
G_Roseburia_RNT	Longevity	0.4491	2.67×10^{-2}
G_Sporobacter_HB	Healthspan	0.2092	3.53×10^{-2}
G_Collinsella_HB	Lifespan	0.3144	4.07×10^{-2}
G_Veillonella_HB	Longevity	0.5578	4.67×10^{-2}
G Genus, *RNT* Rank-normal transformation, *HB* Hurdle binary			

The ageing population has resulted in a larger prevalence of chronic diseases in recent years, and the growing burden on developing-country health-care systems has necessitated research into how to lengthen a healthy lifespan. A multivariate meta-analysis of three European-ancestry GWAS with ageing traits: health span, parental lifespan, and longevity discovered genetic relationships between the three, with longevity being most closely associated to parental lifespan. Furthermore, their research discovered 78 genes linked to these three traits as well as numerous ageing mechanisms. Furthermore, the gut microbiota has been linked to ageing, suggesting new avenues for innovative therapies to promote healthy ageing.

The gut microbiota grows more varied as one gets older, increasing in phylogenetic richness (Fig. 1). When biological age is adjusted for chronological age, however, overall richness declines but particular bacterial taxa linked with unhealthy ageing thrive. As a result, as biological age advances, the homeostatic link between the gut microbiota and the host deteriorates, and gut dysbiosis worsens. [16]

These dysbiotic alterations in the ageing gut can counteract the positive effects of the gut microbiota on nutritional signalling pathways, as well as trigger proinflammatory innate immunity and other pathological diseases. Gut dysbiosis can also disrupt communication between the gut flora and the host via biomolecules, CR-independent signalling pathways, and epigenetic mechanisms, compromising host health and longevity.

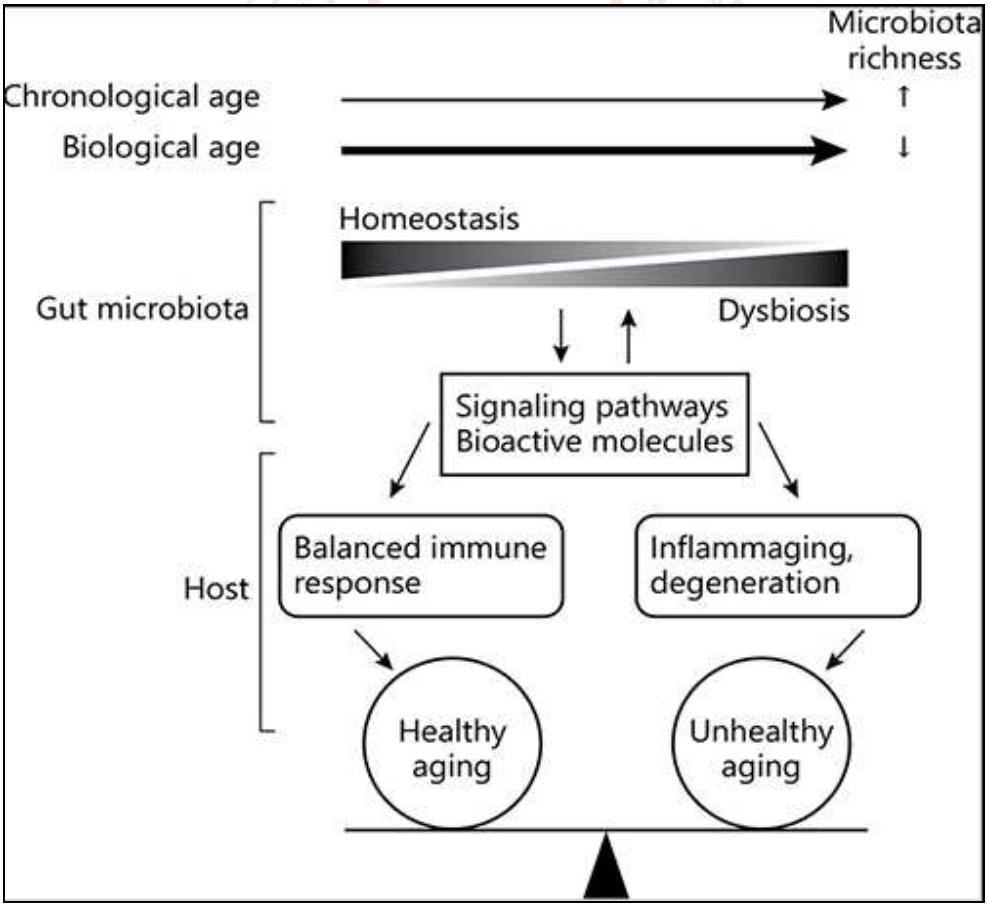

Figure 1: The Gut Microbiota Becomes More Diverse, Increasing in Phylogenetic Richness [17]

Gut dysbiosis and unhealthy ageing are caused by biological ageing. A functional measure of age is a better way to approach ageing biology. An rise in chronological age (in the direction of the arrow) is associated with an increase in the phylogenetic diversity of the gut microbiota, but an increase in biological age has the opposite effect.

The Microbiome in Response to Aging and Pro-Longevity Interventions:

The Aging Gut Microbiome: The Human Side:

Because the microbiota co-evolves with its host, the composition of the microbial community within the digestive tract changes throughout time in response to genetic and environmental cues. Microbial colonisation may begin as early as inutero, according to recent studies that found bacteria in the placenta, amniotic cavity, and umbilical cord. The gut microbiome changes significantly during infancy, which is caused by factors such as birth type, nutrition, antibiotic exposure, maternal food, and environmental influences. The colonisation of microbial species in the gastrointestinal system during the early stages of life has been linked to later health issues in the host organism. Nonetheless, the microbiome composition stabilises after three years, with a profile similar to that of a "adult-like" microbiome. Following sustained microbiome recolonization, nutrition becomes a primary driver affecting the host's microbiome makeup throughout early adulthood. [18]

The Aging Microbiome in Model Organisms:

The baseline microbial composition of the gut microbiota differs between species and taxa. However, substantial remodelling of the gut microbiome during ageing has been documented in a number of model organisms, including Drosophila melanogaster, the African turquoise killifish Nothobranchius furzeri, and mice, similar to what has been observed in humans. [19]

Effects of pro-longevity interventions on the aging microbiome:

Modulation of the microbiota is emerging as a potential mechanism behind many therapies' pro-health and longevity effects (Table 2). Surprisingly, a variety of pro-longevity therapies appear to rejuvenate the microbiota. The proliferation of bacteria from the Lactobacillae taxonomy, which occurs in the context of independent interventions, is a recurring impact. Interestingly, one study found that weight loss in mice during calorie restriction appears to require a healthy microbiota. As a result, it will be critical to evaluate whether microbial community remodelling in the context of longevity therapies is merely a bystander or an active facilitator of pro-health effects. [20]

Table 2: Impact of pro-longevity interventions on the aging microbiome;

Pro-longevity intervention	Organism	Site	Effect on microbiome	Microbiome profiling
Calorie restriction	*M. musculus*	Gut	- Gut microbiota required for CR-induced weight loss - Significant increases in *Lactobacillus*, *Bifidobacterium* - Decreased B/F ratio	V4 16S V3–V4 16S
	R. norvegicus	Gut	- Increase of *Lactobacillus* - Increased B/F ratio - Changes in microbial SCFA production (Increased propionogenesis, decreased butyrogenesis and acetogenesis)	V4 16S Full length 16S Metaproteomics
Dwarfism (*Ames*)	*M. musculus*	Gut	- Increased B/F ratio	V4 16S
Metformin	*C. elegans*	Gut (*food source*)	- Changes the *E. coli* metabolism of folate and methionine - *E. coli* required for longevity extension	N/A
	H. sapiens	Gut	- Increased *E. coli* abundance - Increased production of SCFAs	V4 16S Metagenomics
	M. musculus	Gut	- Increased B/F ratio - Increased abundance of *Lactobacillus*	V4 16S
Rapamycin	*M. musculus*	Oral	- Rejuvenation of the oral microbiome	V4 16S
	M. musculus	Gut	- Increased prevalence of segmented filamentous bacteria - Remodeling of specific OTUs - No change in B/F ratio - Renders microbiome more similar to that of HFD-treated mice	V4 16S Full length 16S (*Sequencing and PhyloChip*)
Resveratrol	*M. musculus*	Gut	- No change in B/F ratio - Reverses HFD-induced changes in bacterial abundances	Full length 16S
Mediterranean diet	*H. sapiens*	Gut	- Increased taxa associated to lower frailty in aged humans - Predicted increase in microbial SCFA production	V3–V4 16S
Acarbose	*M. musculus*	Gut	- Increased abundance in *Muribaculaceae* - Increase in microbial SCFAs, including propionate	V4 16S

CR: Calorie restriction.
B/F: Bacteroidetes/Firmicutes.
SCFA: Short-chain fatty acid.
OTU: Operational taxonomic unit.
HFD: High-fat diet.

Gut Microbiota and Extreme Longevity:

The four age groups showed a good separation on a principal coordinates analysis (PCoA) based on the unweighted Uni Frac distance (Figure 2); indeed, corrected p values obtained by permutation test were <0.05 for all possible comparisons with the exception of groups C versus S. PCo1 separated young subjects (Y) from elderly (E) and long-living individuals (groups C and S; Pearson's $r = -0.61$; $p < 0.001$). As noticeable in the pie charts in Figure 2, the fecal microbiota in all age groups was dominated by just three families: Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae, but their cumulative relative abundance decreased along with aging (77.8% ± 8.5% in Y; 71.1% ± 12.3% in E; 58.7% ± 11.8% in C; 57.7% ± 15.0% in S), highlighting an age-

dependent increasing contribution of subdominant families. Seventy-year-old people (group E) showed similarities with young adults, such as the cumulative abundance of Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae, but started to show also some of the age-associated features observed in centenarians, as demonstrated by the partial overlapping of the samples of the two groups in the PCoA. [21]

Centenarians and 105+ showed very similar relative abundance of Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae, as well as overlapping coordinate values on PCo1 (average PCo1 coordinates –0.36 and –0.33 for group C and S, respectively), but they significantly separated on PCo2 (average PCo2 coordinates −0.38 and 0.38 for groups C and S, respectively; pseudo-F-ratio permutational test; $p < 0.05$), hinting that differences were present between the microbiota structures of these two groups even if the age gap was very small, i.e., 6 years only in average.

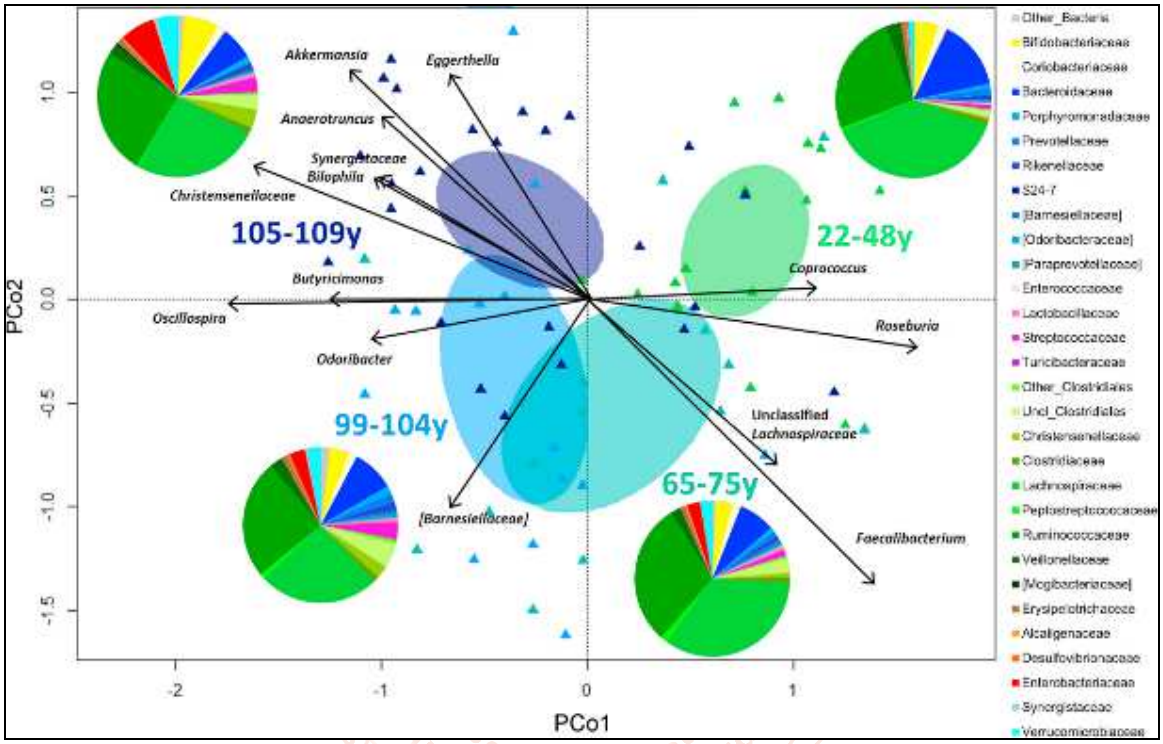

Figure 2: Gut Microbiota Variations across Different Age Groups [22]

Conclusion:

Finally, we presented the longest available trajectory of the human gut microbiota along ageing, with a focus on longevity and extreme longevity, represented by a group of 105+, a demographically very selected group of subjects, as the centenarian-to-105+ ratio is 21.7 (one 105+ for every 21 100+ subjects). We found a core microbiota of highly occurring, symbiotic bacterial groups that remains roughly constant over ageing but varies in the cumulative relative abundance of its members, confirming previously recognised aspects of an ageing microbiota. The gut microbiome has received a lot of interest in the last decade because of the role it plays in host health and disease. While gut microorganisms have been studied for many years, our understanding of the symbiotic relationship that the gut microbiome has with its host and the precise roles it performs is expanding at an exponential rate. The microbiome of the gut develops early in development and remains generally steady into maturity. The literature suggests that age-related changes in the gut microbiome exist, but the lack of well-controlled longitudinal studies makes it difficult to determine whether differences in gut microbiome composition are the result or cause of various age-related conditions observed in both diseased and healthy elderly populations.

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