Gut Microbiome Dynamics as a Determinant of Healthy Longevity: From Aging Signatures to Precision Interventions

Scientific Literature Review

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June 30, 2026

Highlights

- The gut microbiome undergoes a reproducible, age-driven loss of diversity and a shift toward pathobionts that correlates with systemic inflammation, barrier dysfunction, and metabolic decline [1, 2, 3, 4, 5, 6, 7, 8].
- Centenarian microbiomes are not simply youthful; they are enriched in SCFA-producing and mucin-degrading taxa, suggesting that a metabolically versatile community supports resilience rather than age-reversal [9, 10, 11, 12].
- Microbial metabolites such as butyrate act as epigenetic "hormones," modulating host chromatin, immune tone, and mitochondrial function, thereby influencing lifespan in experimental models [13, 14, 15].
- Dysbiosis-driven LPS and bacterial amyloids activate TLR4 and microglial pathways, linking gut ecology to neurodegeneration and cognitive decline [2, 4, 16, 17, 18].
- Precision microbiome therapeutics, guided by high-resolution multi-omics and host-specific signatures, represent a promising frontier for extending healthy human longevity [19, 20, 21, 22, 23].

Abstract

Aging is accompanied by a striking, reproducible remodeling of the gut microbiome that promotes chronic inflammation, barrier dysfunction, and metabolic dysregulation, collectively termed "inflammaging." Here we synthesize large-scale human and experimental studies to show how age-related loss of short-chain fatty acid (SCFA) producers and gain of opportunistic taxa drive epigenetic reprogramming, immune senescence, and neuro-vascular decline. Centenarians harbor a distinct, yet not youthful, microbiome rich in mucin-degrading and SCFA-producing species that underpins resilience rather than reversal of aging. We review mechanistic links between microbial metabolites, host epigenetics, and cardiovascular and neurodegenerative outcomes, and highlight emerging precision microbiome interventions that tailor microbial modulation to individual aging phenotypes. These insights establish the gut microbiome as a modifiable determinant of healthy longevity and chart a path toward translational microbiome therapeutics.

Glossary

Alpha diversity - a measure of microbial richness and evenness within a single sample, often declining with age. **Butyrate** - a short-chain fatty acid produced by certain Firmicutes, acting as an HDAC inhibitor and barrier-strengthening metabolite. **Cardiovascular aging** - age-related decline in vascular function and heart performance, exacerbated by gut-derived metabolites such as TMAO. **Epigenetic "hormone"** - a microbial metabolite that modulates host chromatin (e.g., butyrate influencing histone acetylation). **Enterotype** - a classification of gut microbiota composition dominated by specific genera such as Bacteroides or Prevotella. **Inflammaging** - chronic, low-grade inflammation that emerges with advancing age and is driven partly by microbial dysbiosis. **Microbiome-directed therapeutics** - precision interventions (probiotics, prebiotics, engineered consortia) tailored to an individual's microbial signature. **Neuro-inflammation** - activation of brain immune cells (microglia) by systemic endotoxins or bacterial amyloids originating from the gut. **SCFA producers** - gut

bacteria that ferment dietary fibers into short-chain fatty acids, including *Faecalibacterium*, *Roseburia*, and *Bifidobacterium*. **Trimethylamine-N-oxide (TMAO)** - a gut-derived metabolite linked to atherogenesis and cardiovascular risk. **Widespread gut permeability** - increased intestinal barrier leakiness that permits translocation of microbial products into circulation.

1. Introduction

The human gut microbiome is a dynamic, densely populated ecosystem that evolves predictably across the lifespan, yet its functional relevance to aging remains incompletely understood. Cross-sectional and longitudinal studies consistently report a gradual loss of alpha diversity from infancy to senescence, accompanied by depletion of SCFA-producing commensals such as *Bifidobacterium* and *Akkermansia* and a concomitant rise in potentially pro-inflammatory taxa including *Clostridiaceae* and *Enterobacteriaceae* [1, 2, 3]. These compositional shifts mirror physiological markers of aging-diminished gut barrier integrity, heightened systemic inflammation, and metabolic derangements-suggesting a mechanistic link between microbial community drift and host biology [5, 6, 7, 24, 25]. Despite this correlative evidence, the directionality of the microbiome-inflammaging relationship remains contested. Experimental transfer of aged donor microbiota to germ-free mice recapitulates features of inflammaging, implying causality, whereas human longitudinal data reveal that inflammatory markers can precede dysbiosis, hinting at bidirectional influence [6, 7, 26]. Resolving this causality requires integrating multi-omics, mechanistic studies, and interventional trials that manipulate the microbiome and monitor host epigenetic, immune, and neuro-vascular readouts. A salient question is whether the gut microbiota of exceptionally long-lived individuals simply reverts to a youthful state or embodies a distinct, resilient configuration. Centenarian cohorts across diverse geographies consistently show a Bacteroides-dominated enterotype that is more even and stable, enriched in mucin-degrading and SCFA-producing taxa, yet not a simple return to early-life signatures [9, 10, 11, 12]. These observations underscore the possibility that a metabolically versatile microbiome scaffolds host resilience rather than merely mirroring age. Mechanistically, microbial metabolites, particularly SCFAs, act as epigenetic modulators that shape host chromatin and immune responses, while dysbiosis-driven LPS and bacterial amyloids propagate neuro-inflammation via TLR4 and microglial activation [2, 4, 13, 16, 17, 18]. Cardiovascular aging is likewise linked to microbial metabolites such as TMAO, which promotes atherogenesis, and to loss of SCFA-producing taxa that diminish vascular protection [15, 27, 28]. These insights converge on a unifying hypothesis: that the gut microbiome is a pivotal, modifiable determinant of the aging phenotype. In this review, we first outline the foundational age-associated shifts in microbial composition and function. We then dissect the divergent microbial signatures of healthy versus unhealthy longevity, followed by a mechanistic appraisal of how dysbiosis fuels inflammaging. Subsequent sections explore metabolic-epigenetic crosstalk, neuro-degenerative modulation, cardiovascular implications, and lifestyle drivers of microbiome health in older adults. Finally, we evaluate precision microbiome therapeutics and chart future directions for multi-omics-enabled, personalized aging interventions. Together, these themes illustrate how the gut microbiome not only reflects but actively shapes the trajectory of human longevity.

2. Foundations of the Gut Microbiome-Ageing Nexus

Gut microbiota composition and function evolve in a strikingly reproducible manner across the human lifespan, yet the mechanistic links that tether these microbial shifts to the biology of ageing remain only partially charted. Large-scale cross-sectional studies demonstrate a gradual decline in alpha diversity from infancy to old age, accompanied by loss of short-chain fatty acid (SCFA) producers such as *Bifidobacterium* and *Akkermansia* and a corresponding rise in potentially pro-inflammatory taxa, including *Clostridiaceae* and *Enterobacteriaceae* [1, 2, 3]. Longitudinal analyses in Dutch cohorts confirm that these compositional trends are not merely cohort effects, but reflect a continuous drift in the microbial community structure that parallels physiological markers of ageing, such as diminished gut barrier integrity and heightened systemic inflammation [24, 25]. The convergence of these data underscores a core "aging phenotype" at the microbiome level: a loss of protective commensals and a gain of opportunistic organisms that can perturb mucosal homeostasis.

Mechanistic interrogation of this phenotype implicates several host-microbe axes. First, the gut barrier becomes increasingly permeable with age, a phenomenon that correlates with dysbiosis-driven depletion of mucin-degrading commensals and diminished SCFA production [3, 25]. SCFAs, particularly butyrate, sustain tight junction integrity and modulate epithelial turnover via histone deacetylase inhibition and GPR109A signalling; their loss permits translocation of bacterial endotoxin, fueling systemic "inflammaging" [3, 29]. Second, the aging immune system exhibits a skewed Th17/Treg balance, in part driven by microbial metabolites and surface antigens. Studies show that aged mice have increased gut Enterobacteriaceae and reduced *Akkermansia*, leading to reduced butyrate and impaired Treg induction, which in turn amplifies mucosal inflammation and metabolic dysregulation [30]. Complementary work in humans demonstrates a similar shift toward pro-inflammatory taxa coincident with reduced mucosal regulatory cytokines, reinforcing the bidirectional crosstalk between the microbiome and the aging immune system [31, 32].

Beyond barrier integrity, microbiota-host metabolic signalling emerges as a pivotal lever in the ageing process. Age-associated increases in microbial bile acid (BA) deconjugation alter the circulating BA pool, shifting the ratio of hydrophobic to hydrophilic species and activating hepatic FXR and intestinal TGR5 pathways that regulate glucose and lipid metabolism [29]. Elevated taurocholic acid in older adults correlates with shorter life expectancy, suggesting that altered BA signalling may accelerate metabolic decline independent of overt disease [29]. Parallel alterations in carbohydrate-active enzymes (CAZymes) have been reported in centenarians, who retain a higher abundance of saccharolytic genes that support SCFA synthesis, hinting that preserving metabolic versatility may underpin successful ageing [24, 33].

Genetic and epigenetic interfaces provide further depth to these observations. Host DNA methylation and histone modifications are modulated by microbial metabolites, notably SCFAs, which can inhibit histone deacetylases and alter chromatin accessibility in intestinal epithelial cells and immune populations [34]. In ageing, the epigenetic landscape becomes increasingly plastic, and microbial signals may act as contextual cues that either reinforce or destabilise age-related gene expression programmes. While causality remains to be firmly

established, Mendelian randomisation studies point toward a directional influence of gut microbiota composition on biological ageing metrics, reinforcing the hypothesis that the microbiome is not merely a passenger but an active driver of the ageing phenotype [35].

Collectively, these data delineate a mechanistic framework in which age-related microbial shifts precipitate barrier dysfunction, immune senescence, metabolic reprogramming, and epigenetic drift, thereby amplifying systemic decline. The concordance of human cohort studies with mechanistic insights from animal models and in-vitro systems builds a compelling case for targeting the gut microbiota as a means to attenuate the hallmarks of ageing. Future work must resolve the relative contributions of diet, medication, and genetics to these microbial trajectories, but the emerging narrative is clear: the gut microbiome constitutes a dynamic, mechanistically tractable nexus that links environmental exposures to the biology of longevity.

3. Microbial Signatures of Healthy vs. Unhealthy Longevity

Centenarians represent the pinnacle of healthy human ageing, yet their gut microbiomes do not simply revert to a youthful state. Rather, longitudinal profiling of 1 575 individuals from Guangxi, China, showed that centenarians possessed a Bacteroides-dominated enterotype that was more even, stable, and less pathobiont-rich than that of older adults, and these youth-associated signatures were reinforced over 1.5 years in those who remained well [9]. Similar observations were reported in Italian, Japanese, and Indian centenarian cohorts, where increased Ruminococcaceae, Bifidobacterium, and Akkermansia spp. were consistently enriched, whereas Faecalibacterium prausnitzii and Eubacterium rectale were depleted [10, 11, 12]. This pattern contrasts with the classic "age-related loss of diversity" seen in older adults, which is often characterised by a rise in Proteobacteria and a loss of SCFA-producing taxa [4, 5]. The preservation of diversity and the enrichment of mucin-degrading and SCFA-producing members in centenarians suggest that a robust, metabolically versatile community may scaffold host resilience rather than simply mirror a youthful profile [9, 36].

The functional capacity of these communities further underscores their protective potential. Metagenomic analyses revealed that centenarian microbiomes possess a higher abundance of genes for central carbon metabolism, glycolysis, and fermentation to short-chain fatty acids, but a reduced complement of carbohydrate-degrading enzymes for complex fibers and galactose [36]. In tandem, the same datasets showed heightened xenobiotic-degradation pathways, perhaps reflecting long-term exposure to diverse dietary compounds and the need for detoxification [37]. The presence of methanogenic archaea such as Methanobrevibacter smithii, which forms a stable network with bacterial partners, was also more pronounced in centenarians and linked to a complex, resilient microbial ecology [38]. These functional signatures likely contribute to gut barrier integrity, anti-inflammatory signalling, and metabolic homeostasis, all of which are critical for preserving healthspan.

Sex and lifestyle further refine the microbial landscape of longevity. In Hainan, male centenarians exhibited higher alpha diversity and a distinct species-level profile, including 31 male-enriched and 7 female-enriched taxa, reflecting sex-specific host-microbe interactions

[39]. Urban-village comparisons in South Korea revealed that longevity villages had higher Firmicutes and Lactobacillus, whereas urban elders had more Bacteroidetes, underscoring the role of diet and environment in shaping long-lived microbiomes [40, 41]. These data collectively argue that the "healthy-longevity" microbiome is not a single, static state but a spectrum shaped by genetics, sex, diet, and social context, yet consistently enriched for SCFA producers, mucin degraders, and low-inflammatory taxa.

Despite this convergence on key taxa, some inconsistencies remain. While Biagi et al. reported a depletion of core Bacteroides and Prevotella in extreme ageing, other studies found these genera to be retained or even increased in centenarians, suggesting that the relative abundance of Bacteroides may be more reflective of dietary protein intake than age per se [9, 42]. Moreover, the presence of Escherichia and other Proteobacteria in some centenarian cohorts challenges the assumption that a low-pathobiont signature is universally protective [41]. These discrepancies highlight the need for longitudinal, multi-omics studies that can disentangle cause from consequence and account for individual health status, as proposed by recent reviews that emphasise the importance of biological age over chronological age [43, 44].

In summary, microbial signatures of healthy longevity consistently feature high diversity, enrichment of SCFA-producing and mucin-degrading taxa (Bacteroides, Ruminococcaceae, Bifidobacterium, Akkermansia), and a stable archaeal network centred on M. smithii. Functional potentials skewed toward central carbon metabolism, xenobiotic degradation, and short-chain fatty acid production, coupled with reduced pathogenicity, delineate a microbiome that may scaffold host resilience. Variations in sex, diet, and geography modulate these signatures, underscoring that the "healthy-longevity" microbiome is a dynamic, context-dependent ecosystem rather than a single archetype.

4. Inflammaging and Microbial Dysbiosis: Causal or Consequence?

Inflammaging is the chronic, low-grade inflammatory milieu that emerges with advancing age, driven by a confluence of immune senescence, metabolic dysregulation, and microbiota-mediated signals. The gut microbiome (GM) is now recognised as a pivotal contributor to this state, yet the directionality of the relationship remains debated. Several longitudinal human studies describe a progressive loss of alpha diversity, depletion of short-chain fatty acid (SCFA) producers such as *Faecalibacterium* and *Roseburia*, and enrichment of proteobacterial and pathobiont taxa that correlate with serum cytokines (e.g., IL-6, TNF-alpha) [6, 7, 26]. These associations suggest a mechanistic link whereby diminished SCFA production reduces histone acetylation and anti-inflammatory signaling, whereas increased proteobacterial lipopolysaccharide (LPS) permeates a compromised epithelial barrier, engaging TLR4 and driving NF-kappaB-dependent cytokine release [7, 8]. Importantly, these signatures persist even after adjusting for diet, medication, and comorbidities, hinting at an intrinsic age-driven shift in the microbial community.

Conversely, experimental evidence demonstrates that age-associated dysbiosis can be both a consequence and a driver of inflammaging. Germ-free (GF) mice receiving fecal microbiota

from aged donors develop heightened systemic inflammation, increased IL-1beta, IFN-gamma, and reactive oxygen species (ROS) relative to GF controls, while TLR4-deficient recipients remain protected [45, 46]. These data establish a causal pathway wherein age-specific microbial patterns-rich in LPS-producing taxa and depleted of SCFA producers-activate innate immune sensors and amplify sterile inflammation. Human Mendelian randomization (MR) studies further support a directional effect of the microbiome on biological aging, identifying gut taxa that causally accelerate epigenetic age acceleration and frailty [35, 47]. Nevertheless, the magnitude of these effects and whether they operate uniformly across populations remain uncertain, reflecting heterogeneity in cohort genetics and environmental exposures.

The bidirectional interplay becomes evident when considering barrier dysfunction. Aging is accompanied by increased gut permeability, evidenced by elevated serum lipopolysaccharide-binding protein (LBP) and decreased mucosal IgA [7]. Reduced IgA-mediated targeting permits pathobiont expansion and translocation, perpetuating systemic inflammation. Simultaneously, chronic low-grade inflammation can further erode tight-junction proteins and mucin layers, creating a feedback loop that reinforces dysbiosis [46, 48]. Notably, interventions that restore barrier integrity-such as prebiotic fibers that enrich *Akkermansia*-correlate with decreased circulating cytokines and improved metabolic markers in older adults, underscoring the mechanistic reciprocity [49].

Microbial metabolites provide additional mechanistic granularity. SCFAs, particularly butyrate, activate GPR41/43 and inhibit histone deacetylases, dampening NF-kappaB signalling and promoting regulatory T-cell differentiation [6, 7]. Conversely, age-associated increases in indole-propionic acid and other tryptophan metabolites, produced by *Clostridium* spp., can activate the aryl hydrocarbon receptor (AhR), skewing immune responses toward a pro-inflammatory phenotype [6]. The balance between these metabolites appears to shift with age, tipping toward an AhR-driven pro-inflammatory axis that sustains inflammaging. Moreover, microbial production of trimethylamine-N-oxide (TMAO) rises in aged cohorts, linking the GM to systemic oxidative stress and cardiovascular risk, further intertwining metabolic and inflammatory pathways [45].

Despite robust associations, causality in humans remains challenging to prove. Many observational studies rely on cross-sectional designs, limiting inference about temporal precedence. Intervention trials using probiotics, prebiotics, or fecal microbiota transplantation (FMT) provide more direct evidence: a 12-week probiotic regimen (Lactobacillus acidophilus, L. casei, Bifidobacterium bifidum, Lactobacillus fermentum) improved cognition and metabolic status in AD patients, while FMT from young to old mice reversed age-related gut, eye, and brain inflammation [46, 50]. Yet, the durability of these effects, optimal strains, and dosing regimens remain to be defined, and results are mixed across disease phenotypes. Additionally, the gut-brain axis introduces further complexity; microbial products such as SCFAs can cross the blood-brain barrier, modulate microglial activation, and influence neuroinflammation, potentially feeding back into systemic immune status [51, 52].

In summary, the evidence converges on a model in which age-driven microbial shifts-loss of SCFA producers, gain of LPS-rich proteobacteria, altered metabolite profiles-directly engage innate immune receptors, compromise barrier integrity, and sustain a self-propagating

inflammatory loop. However, the interplay is bidirectional: inflammaging can further remodel the GM, creating a virtuous (or vicious) cycle that accelerates biological aging. Future work must integrate longitudinal human cohorts with mechanistic animal models, apply causal inference tools such as MR and conditional Granger causality, and refine microbiome-targeted interventions to disentangle the causal web and translate findings into durable, personalized therapies for healthy longevity.

5. Metabolic and Epigenetic Cross-Talk between Host and Microbes in Aging

Microbiome-derived metabolites are increasingly recognized as epigenetic "hormones" that tune host chromatin landscapes across tissues, and this dialogue appears to intensify with age. The most studied conduit is the short-chain fatty acid (SCFA) butyrate, a histone deacetylase (HDAC) inhibitor that reshapes transcriptional programs in intestinal epithelial cells and systemic immune cells alike [13]. Butyrate's capacity to hyperacetylate histone H3 lysine 27 in colonic mucosa has been shown to reinforce barrier integrity and dampen pro-inflammatory NF-kappaB signalling, thereby limiting age-associated mucosal senescence [13]. Parallel observations in murine models demonstrate that butyrate supplementation extends healthy lifespan by activating mitochondrial function and antioxidant pathways, underscoring a causal link between microbiome-mediated epigenetic reprogramming and longevity [13]. In contrast, a Western-type diet that suppresses SCFA production abolishes microbiota-dependent histone acetylation in the liver, leading to dysregulated lipid metabolism and accelerated metabolic aging [14]. These data converge on a mechanistic framework where microbial fermentation products serve as co-factors for host epigenetic enzymes, thereby propagating systemic metabolic homeostasis.

Beyond SCFAs, the microbiome supplies one-carbon donors and cofactors that modulate DNA methylation and histone methylation. The gut microbiota's capacity to synthesize and recycle folate, methionine, and vitamin B12 directly influences S-adenosyl-methionine (SAM) availability, the universal methyl donor for DNA and histone methyltransferases [53]. In aged mice, a decline in Firmicutes-derived methanogens correlates with reduced folate production, leading to global DNA hypomethylation in intestinal stem cells (ISCs) and impaired crypt regeneration [54]. Conversely, enrichment of *Clostridium* spp. in long-lived individuals restores folate synthesis, normalizes methylation of ISC-specific genes, and protects against age-related epithelial dysfunction [55]. These observations illustrate a bidirectional epigenome-microbiome axis in which microbial metabolic fluxes fine-tune host epigenetic programmes critical for tissue renewal during aging.

The regulatory interplay extends to non-coding RNAs, particularly microRNAs (miRNAs), whose expression is reshaped by microbial signals. Microbiota-derived indole derivatives suppress miR-155, a key pro-inflammatory regulator, thereby attenuating systemic inflammation in old mice [14]. In human cohorts, age-associated dysbiosis correlates with increased circulating miR-21 and miR-34a, both of which target epigenetic modifiers such as DNMT3A and EZH2, amplifying senescence-associated secretory phenotypes in fibroblasts [56]. These miRNA-epigenetic loops provide a mechanistic explanation for how microbial community shifts can accelerate epigenetic drift and age-related pathologies.

Emerging evidence also implicates RNA N6-methyladenosine (m6A) modifications as a downstream readout of microbiome influence. Bile acids produced by gut bacteria modulate the activity of m6A writers (METTL3/METTL14) in intestinal epithelial cells, altering mRNA stability of genes involved in tight-junction integrity and barrier function [57]. Dysbiosis that shifts bile acid composition toward deoxycholic acid elevates m6A on *Tnf* transcripts, amplifying inflammatory cascades that accelerate aging phenotypes in the gut [58]. These findings expand the epigenetic repertoire affected by the microbiome beyond DNA and histone modifications, highlighting a multilayered regulatory network.

The functional consequences of these epigenetic alterations are reflected in systemic ageing metrics. In physically active middle-aged adults, higher gut microbiome entropy correlates with accelerated epigenetic age as measured by blood-based clocks, suggesting that microbial instability may propagate epigenetic drift that underpins functional decline [59]. Conversely, interventions that enrich anti-inflammatory taxa such as *Akkermansia* and *Bifidobacterium* are associated with decelerated epigenetic ageing and improved physical fitness, underscoring a potential causal pathway from microbial composition to epigenetic rejuvenation [60]. Longitudinal human studies that integrate metagenomic, metabolomic, and epigenomic data are beginning to identify composite signatures that predict longevity and disease risk, offering a roadmap for precision microbiome-epigenetic therapeutics [61].

In sum, the aging gut microbiome orchestrates a network of metabolites-SCFAs, one-carbon donors, bile acids, and indoles-that directly modulate host epigenetic machinery. These interactions reshape chromatin accessibility, DNA and histone methylation, and RNA epitranscriptomic marks, thereby influencing stem cell function, immune tone, and systemic metabolism. The convergence of evidence from germ-free mice, dietary intervention trials, and human epigenetic clock analyses underscores a mechanistic causality rather than mere correlation. Future work that dissects cell-type-specific epigenetic responses to defined microbial metabolites, coupled with longitudinal multi-omics, will be essential to translate these insights into interventions that harness the microbiome-epigenome axis to promote healthy ageing.

6. Microbiome-Mediated Modulation of Neurodegeneration and Cognitive Decline

Microbial modulation of neurodegeneration is now emerging as a central axis linking gut ecology to brain aging. The loss of microbial diversity that accompanies senescence is not simply an epiphenomenon: it unleashes a cascade of metabolic, immunologic and epigenetic alterations that converge on the central nervous system. Early evidence from human cohorts already links specific taxa with cognitive decline. In community-dwelling elders, decreased abundance of Firmicutes such as *Faecalibacterium* and increased Proteobacteria, including *Alistipes* and *Clostridium* spp., predict mild cognitive impairment (MCI) and dementia progression [2, 16]. Parallel animal studies show that transplantation of microbiota from aged donors accelerates cognitive deficits in young recipients, whereas young-donor microbiota rescues hippocampal neurogenesis and memory [17]. These findings support a causal role for the gut community in shaping brain function rather than merely reflecting it.

At the mechanistic level, gut-derived lipopolysaccharide (LPS) and bacterial amyloids are key drivers of neuroinflammation. Dysbiosis enriches LPS-producing *Enterobacteriaceae*, which increase intestinal permeability and allow translocation of endotoxin into the circulation [4, 18]. Systemic LPS then activates Toll-like receptor 4 on microglia, triggering a Th17/Treg imbalance, chronic cytokine production, and impaired blood-brain barrier (BBB) integrity [4]. The resulting neuroinflammation accelerates amyloid-beta (Abeta) deposition and tau phosphorylation, hallmark lesions of Alzheimer's disease (AD) [62, 63]. Consistent with this, mice colonized with *Akkermansia muciniphila* exhibit reduced interleukin-6, diminished BBB leakiness and improved cognition, suggesting that a single taxon can counteract the inflammatory milieu [64]. Importantly, *A. muciniphila* abundance is also correlated with a healthier metabolomic profile, including higher short-chain fatty acids (SCFAs) and secondary bile acids that are known to modulate microglial phenotypes [65].

SCFAs, particularly butyrate, act as histone deacetylase inhibitors, reshaping the epigenetic landscape in both peripheral immune cells and central neurons. Epigenomic studies show that dysbiotic microbiota disrupt DNA methylation patterns in hippocampal genes essential for synaptic plasticity, whereas restoration of a diverse SCFA-rich community normalizes these marks [66]. Moreover, microbial tryptophan metabolites such as indole-3-propionic acid (IPA) penetrate the BBB, modulate serotonergic signaling, and enhance brain-derived neurotrophic factor (BDNF) expression, thereby promoting neuronal resilience [67]. In MCI cohorts, reduced levels of *Prevotella ruminicola* and *Bacteroides thetaiotaomicron* correlate with lower serum IPA and impaired memory performance [68].

Therapeutic modulation of the microbiome offers a tractable avenue to mitigate neurodegeneration. Randomized trials of multi-strain probiotics (Lactobacillus *acidophilus*, *casei*, *bifidobacterium* spp.) improve cognitive scores and reduce systemic IL-6 in AD patients, an effect paralleled by increases in *Faecalibacterium* and *Bifidobacterium* abundance [16, 69]. Fecal microbiota transplantation from young donors to elderly recipients restores hippocampal gene expression profiles and ameliorates working memory deficits in aged mice, underscoring the reversibility of microbial age-related changes [17]. Dietary interventions rich in polyphenols (e.g., Mediterranean diet) shift the microbiota toward a more diverse, SCFA-producing community and are associated with slower cognitive decline in observational cohorts [70, 71]. These interventions converge on common pathways: restoration of barrier integrity, dampening of systemic endotoxemia, and epigenetic reprogramming of neural cells.

Box. Microbial Amyloid and Host Neuronal Sequestration Bacterial amyloids, such as curli from *Enterobacteriaceae*, structurally mimic human Abeta and can seed amyloid aggregation in vitro. In transgenic AD mice, curli-rich feces accelerate plaque deposition and cognitive deficits, whereas curli-deficient mutants fail to do so [62, 63]. This highlights a direct mechanistic bridge between gut proteome and central pathology.

7. Cardiovascular Aging, Gut Microbiota, and Blood-Brain Barrier Integrity

Cardiovascular aging is a cumulative manifestation of chronic low-grade inflammation, oxidative stress and metabolic dysregulation that are increasingly linked to gut microbial perturbations. In aged cohorts, gut dysbiosis is characterized by reduced Firmicutes such as **Faecalibacterium prausnitzii** and increased opportunistic Proteobacteria, a shift that correlates with accelerated epigenetic age and frailty [47, 59]. These compositional changes are not merely epiphenomena; they actively influence cardiovascular pathophysiology via metabolite-mediated signaling. Trimethylamine-N-oxide (TMAO), produced by gut microbes from dietary choline and L-carnitine, has emerged as a potent pro-atherogenic signal that augments platelet hyperreactivity and promotes macrophage cholesterol loading [27, 72]. Conversely, short-chain fatty acids (SCFAs), predominantly butyrate, exert anti-inflammatory and vascular protective effects through GPR43/4 signaling and HDAC inhibition [15, 73]. The loss of butyrate-producing taxa seen in heart-failure (HF) patients and elderly hypertensive models [28, 74] aligns with diminished SCFA flux and heightened systemic inflammation, providing a mechanistic bridge between microbiota and cardiac dysfunction.

The gut-heart axis is bidirectional. Cardiovascular disease itself alters gut permeability and perfusion, fostering a "leaky gut" that allows lipopolysaccharide (LPS) and other microbial products to enter the circulation. Elevated circulating LPS has been repeatedly linked to endothelial activation, hypertension and ventricular remodeling in preclinical models [75, 76]. In spontaneously hypertensive heart-failure rats, microbial functional profiling revealed enrichment of LPS-biosynthetic genes and reduced butyrate synthesis pathways, suggesting that the cardiac phenotype can pre-condition the microbiome toward a pro-inflammatory milieu [28]. Human studies echo this pattern, with HF patients exhibiting lower alpha-diversity and altered beta-diversity that predict clinical outcomes [74, 77]. Importantly, these microbial shifts precede overt cardiac dysfunction in some longitudinal cohorts, implying a potential causal contribution rather than a mere consequence of HF.

Epigenetic mechanisms provide a plausible mechanistic conduit linking gut dysbiosis to cardiovascular aging. Microbial metabolites such as TMAO and SCFAs modulate host DNA methylation, histone acetylation and miRNA expression in endothelial and cardiac cells. For instance, TMAO has been shown to up-regulate pro-inflammatory genes via NF-kappaB activation while concurrently promoting epigenetic silencing of antioxidant pathways [61, 73]. SCFAs, through HDAC inhibition, enhance expression of endothelial nitric oxide synthase (eNOS) and anti-apoptotic genes, thereby preserving vascular tone and myocardial resilience [15]. Epigenetic age acceleration measured by DNA methylation clocks has been linked to both gut microbiota composition and cardiovascular risk, with higher entropy in the microbiome correlating with faster epigenetic aging and reduced fitness [59]. Thus, microbial dysbiosis can accelerate cardiovascular senescence via epigenetic remodeling, creating a feedback loop that exacerbates age-related cardiac decline.

Therapeutic modulation of the gut microbiome offers a promising avenue to mitigate cardiovascular aging and restore blood-brain barrier (BBB) integrity. Fecal microbiota transplantation (FMT) from young to aged animals restores SCFA production, reduces ferroptosis in cardiomyocytes, and improves ejection fraction, underscoring the causal role of the microbiota in cardiac health [15]. Targeted probiotic supplementation with butyrate-producing strains has reduced circulating TMAO, lowered blood pressure, and improved endothelial function in small clinical trials [27, 75]. Dietary interventions high in fiber

and polyphenols promote a resilient microbiota, increasing butyrate output and attenuating epigenetic age acceleration [78, 79]. Moreover, prebiotic-induced SCFA elevation has been shown to reinforce BBB tight-junction protein expression, thereby reducing neuroinflammation and preserving cognitive function in aged mice [66, 77]. These findings collectively suggest that restoring a butyrate-rich microbiota can simultaneously dampen cardiovascular inflammation and protect neural vascular integrity.

Box. **Microbial Metabolites and Epigenetic Crosstalk in Cardiovascular Aging** SCFAs inhibit HDACs, up-regulating eNOS and anti-apoptotic genes in endothelial cells [15]. TMAO activates NF-kappaB, promoting pro-inflammatory cytokine expression and epigenetically silencing antioxidant defenses [61]. Dysbiosis-driven shifts toward LPS-producing taxa exacerbate systemic inflammation, further reinforcing epigenetic changes that accelerate cardiac senescence [75]. Interventions that re-establish butyrate production or suppress TMAO synthesis can reverse these epigenetic signatures and improve cardiovascular outcomes [27, 75].

Despite these compelling associations, causal pathways remain incompletely defined. Many human studies lack longitudinal data and comprehensive metabolomic profiling, limiting inference about temporal relationships [77]. In addition, inter-individual variability in microbiome composition and host genetics complicates the translation of microbial signatures into universal biomarkers [47]. Future work integrating multi-omics, mechanistic animal models and interventional trials will be essential to disentangle the directionality of gut-cardiac communication and to harness the microbiome as a therapeutic target for healthy cardiovascular aging and BBB preservation.

8. Dietary, Exercise, and Environmental Drivers of Microbiome Health in Older Adults

Dietary, exercise, and environmental inputs shape the gut microbiome of older adults in ways that are mechanistically linked to the hallmarks of aging. The age-associated loss of microbial diversity and the rise of pathobiont taxa, such as certain Enterobacteriaceae and opportunistic clostridia, are consistently reported across populations, yet the magnitude and direction of change depend on the nature of the exposure. Dietary fiber, in particular, stands out as a robust driver of SCFA-producing taxa, including *Faecalibacterium prausnitzii* and *Roseburia* spp., which in turn reinforce mucosal barrier integrity and dampen systemic inflammation [4, 49]. In contrast, high-fat or processed-meat diets promote bile-acid-metabolizing *Bilophila* and *Desulfovibrio*, which increase lipopolysaccharide production and gut permeability, fueling inflammaging [80]. The mechanistic link between dietary composition and microbial metabolic output is evident in human studies where Mediterranean-style diets, rich in polyphenols and fibers, enrich *Bifidobacterium* and *Lactobacillus* and elevate circulating butyrate, an epigenetic modulator that suppresses NF-kappaB signaling in macrophages [4, 49].

Exercise exerts a complementary, albeit more variable, influence on the microbiome. Systematic reviews show that aerobic training increases alpha diversity and elevates *Bacteroides* and *Prevotella*, both associated with carbohydrate fermentation and SCFA

production [81, 82]. Resistance training, on the other hand, appears to have a muted effect on overall community structure but can selectively expand *Ruminococcus* spp., which produce lactate and propionate that support muscle protein synthesis [83]. The discrepancy between study outcomes likely reflects differences in exercise modality, intensity, and participant baseline fitness. For instance, a five-week endurance program in men aged 62-76 failed to shift diversity [21], whereas an eight-week combined aerobic-resistance regimen in overweight adults modestly altered the microbiota but did not reach statistical significance in older cohorts [21]. These mixed results suggest that the microbiome's responsiveness to exercise is constrained by age-related reductions in ecological resilience and the need for sustained, high-intensity stimuli to achieve lasting shifts [84].

Environmental exposures further modulate these dietary and exercise effects. Geographic location, encapsulated in the exposome, determines baseline microbial repertoires through differences in climate, sanitation, and cultural food practices. Blue-zone populations, such as those in the Mediterranean and Cilento, show higher *Akkermansia muciniphila* abundance, a mucin-degrading bacterium linked to improved glucose homeostasis and longevity [85]. Conversely, urban living and frequent antibiotic use, common in nursing homes, reduce microbial richness and favor opportunistic taxa, contributing to frailty and increased frailty scores in older adults [86]. Intermittent fasting, a dietary rhythm that transiently reduces gut luminal nutrients, has been shown to induce a rapid expansion of *Lactobacillus* and *Bifidobacterium*, suggesting that temporal patterns of feeding can prime the microbiome for metabolic benefits [87]. The interplay between environmental factors and host genetics further complicates the picture, as host immune senescence limits the capacity to restore microbial balance after perturbation, reinforcing age-related dysbiosis [88].

The mechanistic nexus between these drivers and host physiology often involves microbial metabolites that interface with host signaling pathways. SCFAs, particularly butyrate and propionate, activate G protein-coupled receptors (GPR41/43) on enteroendocrine cells, enhancing GLP-1 secretion and improving insulin sensitivity-key determinants of healthy aging [65]. Short-chain fatty acids also inhibit histone deacetylases in colonocytes, reinforcing mucin production and barrier integrity, thereby reducing systemic endotoxemia that fuels chronic inflammation [86]. Bile acid metabolism, modulated by diet and exercise, influences the farnesoid X receptor (FXR) and G protein-coupled bile acid receptor (TGR5), affecting lipid metabolism and energy expenditure; dysregulated bile acid profiles have been linked to sarcopenia and frailty in older adults [80]. Microbial tryptophan metabolites, such as indole-3-propionic acid, cross the gut-brain axis to modulate neuroinflammation, potentially mitigating cognitive decline that accompanies aging [89]. These metabolite-host pathways underscore how lifestyle interventions can shift microbial composition toward a phenotype that dampens inflammaging and preserves metabolic homeostasis.

Despite these mechanistic insights, evidence remains fragmented and often inconclusive. Many dietary interventions show transient shifts that revert once the feeding pattern is normalized, highlighting the need for sustained, individualized approaches [88]. Exercise studies in older adults are limited by small sample sizes, heterogeneous protocols, and insufficient mechanistic readouts, making it difficult to disentangle causal from correlative relationships [83, 90]. Moreover, the bidirectional nature of the microbiome-environment interaction-whereby microbial communities influence nutrient absorption and energy balance,

which in turn modulate physical activity-creates a complex feedback loop that is only partially understood [91]. Future longitudinal, multi-omic studies that track dietary patterns, physical activity, environmental exposures, and host metabolic and epigenetic markers will be essential to delineate the causal pathways and to develop precision nutrition and exercise prescriptions that harness the microbiome for healthy longevity.

9. Precision Microbiome-Directed Therapeutics for Healthy Longevity

Targeted manipulation of the gut microbiome has evolved from broad-scope "prebiotic or probiotic" concepts to precision interventions that integrate host-specific microbiome profiling, mechanistic insight, and regulatory safeguards. This paradigm shift is driven by the recognition that interindividual microbiome diversity, driven by genetics, diet, and age-related shifts, profoundly influences therapeutic efficacy and safety, especially in older adults where the microbiome's role in cardiometabolic, neurodegenerative, and immune senescence is most pronounced [19, 20, 21]. The convergence of high-resolution metagenomics, metabolomics, and host transcriptomics now permits the design of microbiome-directed therapeutics that are tailored to a patient's microbial signature and disease context.

Mechanistic precision begins with the identification of microbial taxa that modulate aging phenotypes. Short-chain fatty acids (SCFAs), chiefly butyrate, are central to barrier integrity, anti-inflammaging, and mitochondrial homeostasis [22, 92]. Engineered consortia delivering butyrate-producing Firmicutes (e.g., Faecalibacterium prausnitzii, Roseburia spp.) or delivering prebiotics that selectively enrich these taxa have shown promise in preclinical models of metabolic dysfunction and neurodegeneration [22, 23]. However, human trials reveal heterogeneous responses, likely due to baseline enterotype variation and host genetics [21, 93]. Accordingly, clinical studies increasingly incorporate microbiome stratification as an eligibility criterion or as a stratified analysis endpoint, a strategy advocated in the melanoma phase-Ib trial that matched antibiotic pre-conditioning to baseline diversity [93].

Beyond SCFAs, microbial metabolites such as trimethylamine-N-oxide (TMAO) and bile acid derivatives exert cardiometabolic and neuroinflammatory effects that are age-dependent [92, 94]. Precision therapeutics now target metabolic pathways through small-molecule inhibitors, dietary modulation, or microbial editing. For instance, the use of a synthetic bile acid receptor agonist, delivered via a defined microbial chassis engineered to overproduce deoxycholic acid, has reduced atherosclerotic plaque burden in murine models of accelerated aging, illustrating how engineered microbes can be leveraged to modulate host signaling pathways [95]. The safety of such genetically modified organisms (GMOs) is a key regulatory concern; recent guidelines propose a 12-month safety assessment aligned with phase III trials to mitigate risks of horizontal gene transfer or toxin production [96, 97].

Clinical translation also hinges on the delivery vehicle. Fecal microbiota transplantation (FMT) remains the most potent but least controllable intervention. Advances in defined consortia, such as the 8-species VE303 and the spore-enriched SER-109, provide reproducible, scalable alternatives that preserve functional diversity while minimizing

pathogen transfer [98, 99]. Phase-3 trials of VE303 for recurrent Clostridioides difficile infection have demonstrated non-inferiority to donor stool, underscoring the feasibility of moving from unfiltered to defined microbiota therapeutics in vulnerable populations [99]. Yet, even defined consortia face challenges of engraftment and durability; longitudinal monitoring of microbiome composition post-FMT remains essential to correlate microbiota stability with clinical outcomes [100, 101].

Emerging platforms combine microbial editing with host-directed interventions. CRISPR-based bacteriophage therapies that selectively eliminate pro-inflammatory Enterobacteriaceae while sparing commensals have shown efficacy in murine models of chemotherapy-induced cardiotoxicity, a condition linked to dysbiosis-mediated oxidative stress [102]. Integrating phage therapy with dietary prebiotics that promote Lactobacillus and Bifidobacterium expansion may synergistically restore the anti-inflammaging milieu, but robust human trials are scarce [103]. Similarly, next-generation probiotics (NGPs) that secrete anti-inflammatory cytokines or produce polyamines are in early-phase trials; their mechanistic rationale is rooted in epigenetic modulation of host immune cells via microbial metabolites [104, 105]. The translation of NGPs to the clinic requires meticulous safety profiling, given their potential for persistent colonization and horizontal gene transfer [96].

Regulatory and methodological harmonization is a bottleneck. Standardized protocols for sample collection, sequencing depth, and bioinformatic pipelines are needed to ensure reproducibility across studies that compare taxonomic and functional changes pre- and post-intervention [106, 107]. Moreover, the lack of validated companion biomarkers hampers patient selection and outcome prediction. Recent efforts to develop predictive models based on machine learning, trained on multi-omics datasets, show that baseline microbiome signatures can forecast responders to dietary prebiotic trials and to immunotherapy in cancer patients, suggesting a transferable framework for longevity interventions [21, 93]. The adoption of such precision frameworks, exemplified by the PRIME roadmap, will accelerate the design of pragmatic, biomarker-guided trials that can assess real-world efficacy in elderly cohorts [108].

In conclusion, precision microbiome-directed therapeutics for healthy longevity rest on a triad of advances: (i) mechanistic dissection of age-relevant microbial functions (SCFAs, bile acids, TMAO); (ii) engineered microbial consortia and phage tools that enable safe, targeted modulation; and (iii) rigorous, biomarker-guided clinical trial designs that account for individual variability. While preclinical evidence is robust, translational success will hinge on overcoming regulatory, safety, and methodological hurdles, thereby turning the gut microbiome from a prognostic marker into a therapeutic lever for extending healthspan.

10. Future Horizons: Multi-Omics, Exposome, and Personalized Aging Interventions

The future of microbiome-driven longevity hinges on a systems-level view that fuses longitudinal human data with high-resolution omics, environmental exposure, and individualized therapeutics. First, the sheer scale of multi-omics integration is already evident: longitudinal cohorts of >10,000 adults have been profiled for gut metagenomics,

plasma metabolites, and clinical phenotypes, revealing age-associated microbial species and metabolic clusters that predict cardiovascular risk and frailty [109]. In parallel, the advent of comprehensive microbial isolate libraries paired with longitudinal multi-omics data provides a mechanistic bridge between taxonomic shifts and functional outputs, enabling inference of in-vivo selection pressures and microbial metabolic fluxes across the lifespan [110]. These resources collectively demonstrate that aging is accompanied by a loss of core commensals (e.g., *Faecalibacterium prausnitzii*), a rise in opportunists (e.g., *Streptococcus* spp.), and a shift toward bile-acid and xenobiotic-degradation pathways that may fuel low-grade inflammation (exposome-driven chronic stress) [55, 111]. Yet, these associations are predominantly correlative; establishing causality will require controlled, time-resolved interventions and mechanistic readouts, such as measuring siderophore-mediated iron competition or SCFA production in vivo.

The exposome adds a crucial third dimension. Studies of long-lived populations (e.g., the Jiaoling county cohort) show that metabolite trajectories differ markedly from those of ordinary elderly, with enrichment of anti-inflammatory metabolites and distinct microbial taxa like *Bacteroides stercoris* [55]. Likewise, exposome analyses of Blue Zone populations underscore that environmental quality, diet, and psychosocial factors collectively sculpt the gut microbiome, which in turn mediates resilience to age-related decline [85]. Integrating exposomic data (adductomics, metabolomics, and epigenomics) with microbial profiles can reveal dynamic feedback loops: for instance, chronic oxidative stress may promote *Clostridium* spp. expansion, which produces pro-inflammatory metabolites that accelerate epigenetic aging [112]. However, current exposome-microbiome datasets are sparse, often cross-sectional, and limited by short-term exposure windows, leaving a knowledge gap in how lifetime exposure trajectories shape the microbial ecosystem and aging phenotypes.

Artificial intelligence and machine learning are becoming indispensable for navigating this data deluge. Deep neural networks have been trained on multi-omics cohorts to predict individual biological age, outperforming single-omic markers by incorporating microbiome, cytokine, and metabolite signals [112]. In aging research, machine learning pipelines (e.g., random forests and permutation-based feature selection) have identified microbial signatures that distinguish healthy from unhealthy longevity with high accuracy [31]. Yet, the interpretability of these models remains a challenge; explainable AI approaches are needed to link statistical features to mechanistic pathways such as SCFA-mediated GPR43 signaling or microbial bile-acid deconjugation. Moreover, AI can guide the design of personalized interventions by simulating the impact of prebiotic, probiotic, or diet modifications on predicted aging trajectories.

Personalized microbiome-directed therapeutics are the logical next step. Precision probiotics, tailored to an individual's baseline microbiome, have shown promise in modulating cognitive outcomes in older adults by targeting specific taxa such as *Lactobacillus* and *Bifidobacterium* [113]. Similarly, fecal microbiota transplantation (FMT) coupled with next-generation probiotics ("drug-the-bug" strategies) has been proposed to re-establish a healthy microbial core in patients with cardiovascular disease, leveraging the gut-heart axis mediated by microbial metabolites like TMAO and SCFAs [114]. However, the safety, efficacy, and durability of such interventions are still under investigation, and rigorous, standardized protocols are needed to ensure reproducibility across diverse populations,

especially institutionalized or frail elders who are under-represented in current studies [49]. Integrating longitudinal monitoring of microbial dynamics with clinical endpoints (e.g., frailty index, mortality) will provide the evidence base required for regulatory approval and clinical adoption.

Finally, the convergence of multi-omics, exposomics, and personalized therapeutics necessitates a new framework for aging research. Multi-omic aging clocks that incorporate microbiome features have been shown to predict mortality and disease risk more accurately than traditional biomarkers alone [115]. By constructing individual "ageotypes" based on metabolomic, proteomic, and microbial signatures, researchers can identify early shifts toward disease-like configurations and intervene before clinical decline. Boxed deep-dives such as "Microbiome-Metabolite-Immune Triad" could elucidate how specific microbial metabolites (e.g., indole derivatives, butyrate) modulate host immune signaling and epigenetic aging. In sum, the future hinges on integrating these data streams into a coherent, mechanistically transparent platform that can translate microbiome insights into precise, evidence-based interventions to extend healthspan and longevity.

Concluding Remarks and Future Perspectives

The convergence of longitudinal human epidemiology, mechanistic animal work, and emerging microbiome-directed therapeutics has begun to map the gut microbiome's contribution to human longevity. Robust evidence supports a consistent "ageing phenotype" of the microbiome: progressive loss of alpha diversity, depletion of SCFA-producing commensals such as *Faecalibacterium* and *Bifidobacterium*, and enrichment of opportunistic Proteobacteria and lipopolysaccharide-producing taxa [1, 2, 3, 6, 7, 26]. These shifts correlate strongly with hallmarks of ageing-including increased intestinal permeability, systemic inflammation, and epigenetic drift-suggesting a causal role for dysbiosis in driving inflammaging [7, 8, 14]. Moreover, centenarian studies reveal that a preserved, metabolically versatile microbiome-rich in SCFA producers and mucin-degraders-appears more protective than a simple return to a youthful community [9, 12, 36]. Such data underscore the notion that functional resilience, rather than mere taxonomic youthfulness, may scaffold healthy longevity.

Mechanistically, SCFAs, especially butyrate, emerge as pivotal microbial metabolites that act as epigenetic "hormones." Through HDAC inhibition and GPR43/4 signalling, butyrate fortifies epithelial barrier function, dampens NF-kappaB-driven cytokine production, and supports mitochondrial health, all of which translate into extended healthy lifespan in preclinical models [13, 15, 92]. Conversely, microbial production of TMAO and LPS fuels atherosclerosis and neuroinflammation, linking gut dysbiosis to cardiovascular and neurodegenerative pathology in the elderly [27, 72, 77]. The bidirectional gut-heart and gut-brain axes, therefore, provide mechanistic scaffolds that connect microbial metabolites to systemic ageing phenotypes.

Despite these advances, significant gaps remain. First, most human associations are cross-sectional or observational; intervention studies that alter the microbiome and track longitudinal health outcomes are scarce and often yield heterogeneous results [21, 22].

Second, the causal direction between dysbiosis and inflammaging is still contested: while germ-free mice receiving aged microbiota develop inflammatory phenotypes, whether reverse causation (age-driven host changes selecting for dysbiosis) dominates is unclear. Third, precision microbiome therapeutics are in their infancy; translating taxa-specific interventions from mouse models to humans has proven challenging due to interindividual variability in microbiome composition and immune status [19, 20, 21]. Finally, the interaction between host genetics, environmental exposures (exposome), and microbiome dynamics across the lifespan is poorly quantified, limiting our ability to predict who will benefit most from microbiome-based interventions.

The most promising directions combine high-resolution, longitudinal multi-omics with targeted, mechanistically informed therapeutics. Engineering butyrate-producing consortia or prebiotics that selectively enrich these taxa could restore barrier integrity and epigenetic homeostasis in older adults [22, 23]. Parallel efforts to modulate TMAO-producing pathways-through dietary modification, microbiome editing, or pharmacologic inhibition-may reduce cardiovascular risk in the ageing population [27, 74]. Importantly, integrating exposomic data will allow us to disentangle environmental drivers of microbial shifts from intrinsic ageing processes, paving the way for truly personalized microbiome interventions. Ultimately, a systems-level framework that links microbiome dynamics to host metabolism, immunity, and epigenetics will be essential to translate these insights into clinically actionable strategies that promote healthy ageing and extend the human healthspan.

Outstanding Questions

- What is the precise causal direction between age-associated dysbiosis and systemic inflammaging, and can manipulating the microbiome reverse established inflammatory states?
- How do host genetic and epigenetic factors modulate individual responses to microbiome-targeted interventions in older adults?
- Which specific microbial metabolites (beyond SCFAs and TMAO) serve as reliable biomarkers and therapeutic targets for age-related cognitive decline?
- Can precision microbiome therapeutics be safely and effectively scaled to diverse aging populations with varying comorbidities and medication regimens?
- How does the exposome interact with microbiome shifts to influence the trajectory of healthy versus unhealthy ageing across different ethnic and socioeconomic groups?
- What are the optimal longitudinal study designs and endpoint measures needed to establish causality and therapeutic efficacy of microbiome modulation in human ageing?

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