The gut microbiome as a modulator of healthy ageing

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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. In this Review, we explore targeted studies of the gut microbiome of older individuals and general cohort studies across geographically distinct populations. We also address the promise of the targeted restoration of microorganisms associated with healthier ageing.

Everyone ages but the deleterious effects of ageing on physical and intellectual function are not experienced uniformly. Delayed age-related decline, or ‘healthy’ ageing, is evident in many people. Determinants of healthy ageing include genetic, environmental and lifestyle factors, the latter presenting an opportunity for intervention. The microbiome transduces environmental signals, conditions host immune, metabolic and neurological function, and modifies the risk of disease, including age-related diseases. However, the microbiome has a reciprocal relationship with age: it changes as the host ages and is altered in age-related disease, but it also modifies age-related impairment of the host.

The importance of these relationships is underscored by changing global demographics. It is projected that, in the next 30 years, the number of people aged ≥65 years will more than double, reaching 1.5 billion globally, the majority of whom will be in less-developed countries. Therefore, costs of health care will escalate enormously unless the determinants of healthy ageing are comprehensively addressed. While stressors, such as the disproportionate effects of COVID-19 on older people, reveal the fragility of healthy ageing, it is the tenuousness or lack of physiological reserve in older people that may enable minor alterations relative to a non-diseased state in the microbiome to have a significant beneficial or negative influence on physical and cognitive function. In this respect, ageing presents an opportunity, tantamount to a human model for calibrating microorganism–host interactions in health and disease.

We have previously addressed the elements of a healthy microbiome while highlighting that a single universal healthy microbiome configuration does not exist. In this Review, we focus on the dynamic relationship between the gut microbiome and ageing, including age-related disease, and explore prospects for microbial manipulation to promote healthy ageing. Throughout this Review, we specifically concentrate on the gut microbiome but the concepts are likely to be applicable to microbial communities at other body sites.

The gut microbiome in health and disease

Animals harbour complex communities of gut microorganisms that show host specificity in their composition and function, and which co-evolved with their multicellular hosts, shaped by habitual diet. In the human gut, the resident community of microorganisms reputedly numbers approximately 2,000 bacterial species and might outnumber the human cell count and number of different coding genes. Interest in the human gut microbiome accelerated when culture-independent methods revealed that the microbiome was different in patients with a range of disorders compared with healthy individuals (reviewed in REF and summarized in Table 1). However, few mechanisms that link pathophysiology with specific microbial metabolites lost from the normal microbiome or gained by the disease-associated microbiome have been identified, a challenge exacerbated by the difficulty in defining a health-associated microbiome. Despite these challenges, microbiome–health interactions can be assigned to a number of broad categories that are useful for considering (as we do later in this Review) how these relationships might go awry in ageing and what the effect on the host would be.

Metabolic effects. Microorganisms have developed a remarkably broad capacity to use inorganic and organic molecules as nutritional substrates; in the mammalian gut, they can catabolize plant-derived polysaccharides and resistant starches that would otherwise be unavailable to the host. Flint et al. have reviewed how changes in gut microbial metabolism of short-chain fatty acids (SCFAs), vitamins, lipids, gases, cholesterol and atherogenic compounds can alter host susceptibility to obesity and metabolic syndrome, irritable bowel syndrome,
Key points

- The gut microbiome is a transducer of environmental signals, modifies the risk of disease across all age groups and changes with host age.
- Age-related alterations in the gut microbiome are influenced by personal factors, including progressive physiological deterioration, as well as by lifestyle-linked factors such as diet, medication and reduced social contact.
- Age-related and disease-related deterioration in the gut microbiome of older people reflect overlapping interactive but distinct processes.
- Resetting gut microbiome-derived signals of ‘unhealthy’ ageing through personalized or subpopulation-level microbiome-associated interventions is a new area of research informed by large shotgun metagenomics-based studies and data analytics.
- Gut microbiome-based therapeutics for older people will need combined approaches, including dietary intervention with microbial restoration of lost strains.

and cardiovascular disease11. Despite the scale and complexity, analytical advances have catalogued the most abundant microbial metabolites that affect the host (reviewed in REF 12) as well as the microbial enzymes involved. Key metabolites include SCFAs, amino acids, bile acids, vitamins, tryptamine, histamine, serotonin, dopamine, para-cresol and phenylacetylglutamine12. Thus, in addition to contributing to flux in host metabolic pathways, many microbial metabolites can affect the activity of the liver and the endocrine system13.

Age-related influences on the microbiome

Ageing is a progressive loss of homeostasis, impaired function and vulnerability to death. Age-related diseases include infectious, neoplastic, metabolic and degenerative disorders with frailty and cognitive decline. At a fundamental level, the molecular and cellular hallmarks of ageing in mammalians have been identified15 but these are accompanied by changes in the microbiome, which in turn affect the rate of age-related decline (FIG. 1).

Age-related changes in the microbiome are highly variable, influenced by both personal and external environmental factors. For example, the gut microbiome is predictably affected by progressive deterioration in the physiology of the alimentary tract. These changes include increased ageing-associated inflammation, genomic instability, cellular (and mitochondrial) dysfunction, reduced proteostasis and epigenetic dysregulation, which further lead to the onset of chronic diseases, metabolic disorders and impaired gut–brain communication (reviewed in REFs 26,27). The attendant effects on host behaviour and lifestyle (increased frailty, medication intake, surgery, reduced physical activity and quality of diet) can further exacerbate the effects on the gut microbiome. Lifelong personal lifestyles, particularly diet, also shape the composition and function of the microbiome in older people28 but represent opportunities for healthy behaviour change. Less well explored is the influence of social interactions on the composition of the microbiota and how society cares for its older people (FIG. 2).

Increasing evidence suggests that transmission of microorganisms among individuals living in a social group has important health benefits29. While the spread of pathogens within social groups has received close scrutiny, strain tracking studies have shown that commensals and mutualistic microorganisms are also shared within social networks30. The microbiomes of individuals living in the same home tend to have compositional similarities, in comparison with those from people in other households31,32. Household pets can contribute to microbial sharing by acting as vectors of transmission33. Moreover, individuals with larger social networks seem to have more diverse gut microbiomes34. However, the collective microbial metacommunity of a family (the ‘social microbiome’) changes over time, with opportunities for microorganism acquisition diminishing, sometimes abruptly, for older people. Additional change depends on whether the individuals reside alone or in institutional care35 (FIG. 2). Aloneness and loss of group living are among the social changes that have become characteristic of modern socioeconomically developed societies and contrast with the past and with traditional, non-industrialized ethnic groups such as the Hutterites and the Irish Travellers29,36.

Gut microbiome changes with ageing

Microbiome studies focused on older people can be classified into two broad categories: reports of differences in gut microbiome composition related to age per se, and reports of alterations in the microbiome of older people that are associated with particular ageing-linked disorders (detailed in TABLES 2, 3). The main findings...
from the two categories of ageing-related studies, a literature-based identification of distinct groups of taxa that show consistent alterations with ageing as well as between healthy and unhealthy ageing, along with the metabolic capabilities of these taxon groups that can direct the host to either a healthy or an unhealthy ageing trajectory, are described in this section.

The first category of studies provides a picture of how the gut microbiome changes with age in general, notwithstanding the fact that these are not longitudinal studies. Particularly noteworthy are studies of centenarians across various geographies and nationalities. In general, the composition of the gut microbiome of centenarians (studied in countries/regions including Italy, Russia, China and India) is distinguished by a lower abundance of symbionts associated with health in younger age groups (such as Faecalibacterium spp.) and an elevated abundance of both alternative health-associated taxa (such as Akkermansia spp.) as well as disease-associated pathobionts. Gut microbiota genes associated with xenobiotic degradation were noted to be in higher abundance in extreme ageing. Interest in these cohorts stems from the assumption that identifying gut microbiome signatures specific to long-living centenarians might be akin to identifying therapeutic microbiome signatures for longevity or healthy ageing. However, this assumption might not be correct because these are all cross-sectional single snapshots and extreme ageing is not equivalent to healthy ageing. In other words, all apparently healthy centenarians might not be equally healthy and some might have progressed into ageing-linked physiological decline (as summarized in Fig. 1).

Despite reservations about the generalizability of such findings in centenarians, there are striking similarities in the extreme ageing-linked microbiome signatures established across different studies. This is despite wide variation in the demographics of the study populations, ranging from a geographically isolated rural population in India to a wealthy semi-urbanized community in Italy. We and others have also shown that these taxonomic changes overlap with a generic age-associated microbiome variation pattern (Fig. 3). These general ageing-related changes are characterized by a loss of dominant commensal taxa (such as Prevotella, Faecalibacterium, Eubacterium rectale, Lachnospira, Coprococcus and the health-associated genus Bifidobacterium). These taxa appeared to be replaced by a second group of commensals (such as the putatively beneficial Akkermansia, Christensenellaceae, Butyrivimonas, Odoribacter and Butyrivibrio) and pathobionts (such as Eggerthella, Bilophila, Fusobacteria, Streptococcus and Enterobacteriaceae). These microbiome alterations encompass those associated

Table 1  Representative studies linking human conditions to the microbiome

| Condition or disease | Microbiome alteration | Potential or known mechanism | Comments | Refs |
|----------------------|-----------------------|-----------------------------|----------|------|
| Obesity | Greater abundance of pathobionts and Firmicutes | Calorie harvesting, inflammation, modulating satiety, regulating adipogenesis | Controversial microbial links to complex, that is, multifactorial, disease | 137 |
| Type 2 diabetes | As for obesity, with signals related to Prevotella copri and Akkermansia muciniphila | Unclear; liver signalling, branched-chain amino acids? | Initial success with faecal microbiota transplantation not maintained in later studies | 150 |
| Inflammatory bowel disease | Reduced abundance of Christensenellaceae, Coriobacteriaceae, Faecalibacterium prausnitzii; higher abundance of Actinomycetes, Veillonella, Escherichia coli | Products of colonic inflammation stimulate anaerobic respiration, driving microbiome further towards a pro-inflammatory type | Meta-analysis concedes lack of a unifying taxon signature for inflammatory bowel disease; once inflammation is triggered, the microbiome may be irrelevant for treating inflammatory bowel disease | 159,160 |
| Irritable bowel syndrome | Ruminococcus gravis and Lachnospiraceae are more abundant, Bamesiella intestiniformis and Coprococcus catus depleted | Pathophysiology may involve a reduction of luminal pH by excessive fermentation and sensitization of the enteric nervous system by inflammation | Not all patients with irritable bowel syndrome have an altered microbiome; disruption of the diet–microbiome–metabolome connectivity is a feature of those who do | 161,162 |
| Colorectal cancer | Presence of Fusobacterium nucleatum and other oral biofilm-forming pathobionts is a feature of tumour microbiome | Inflammation, DNA breakage, mutagenesis | Microbiome alterations linked to colon cancer relate to known risk factors such as diet and inflammation; microbiome also influences the responsiveness of cancers to checkpoint immunotherapy | 10 |
| Cardiovascular disease | Bacterial taxa capable of generating trimethylamine from carnitine, choline and glycine betaine | Trimethylamine is a substrate for liver production of trimethylamine oxide, an atherogenic metabolite | Initial controversy due to inverse relationship between choline intake and cardiovascular disease but prospects for druggable targets | 7,8,103 |
| Cognitive function, behaviour and mood | Diverse observations and metabolites reported but a catalogue of gene products with neuroactive potential identified | Effects on neurodevelopment, neuroplasticity, degree of myelination, peptide binding to immune cells and vagus nerve endings, other brain signalling effects | Plausible leads but a paucity of compelling human studies | 8,104 |

These studies represent selected examples of conditions or diseases in which the causality of the microbiome as a contributing or mediating factor was demonstrated. The studies and reviews provided are those that describe the mechanism, and the bacteria specified are those that show constant association across studies.
The microbiota plays a crucial role in healthy and unhealthy ageing. As we age, there are changes in the host–microorganism interactions, which can be categorized into healthy and unhealthy ageing. Healthy ageing is characterized by the presence of protective taxa that support the host, while unhealthy ageing is marked by the presence of pathobionts. The microbiome composition changes over time, with specific taxa becoming more abundant or less abundant. These changes are influenced by environmental factors, diet, and lifestyle. Understanding these changes can help in developing strategies to promote healthy ageing.

Fig. 1 | Microorganism–host signalling as a contributor to healthy or unhealthy ageing. Chronological age is accompanied by changes in host–microorganism homeostasis that determine, in part, the rate of physical and cognitive decline. Lifestyle and environmental effects on the microbiota can delay (healthy ageing) or accelerate (unhealthy ageing) deterioration in the host and foreshorten life expectancy.

With ageing in general as well as those associated with ageing-linked decline in health.

Identifying the microbiome elements associated with healthy and unhealthy ageing can be achieved by longitudinal studies tracking individuals over an extensive period of time and by relating the gut microbiome composition measured at intermediate time points to the final physiological or clinical status. A widely used alternative is to adopt a cross-sectional study design that stratifies older populations based on indices of unhealthy ageing as well as of healthy ageing and that identifies the corresponding taxonomic markers. Six groups of microbial taxa were identified based on their disease-linked abundance alterations in different age categories. These groups were referred to as groups G1 (disease-elevated across all age groups), G2 (elevated in multiple diseases only in older individuals aged ≥60 years), G3 (elevated across multiple diseases only in young or middle-aged people aged between 20 and 60 years), L1 (depleted in multiple diseases across all age groups), L2 (depleted in multiple diseases only in older individuals aged ≥60 years) and L3 (depleted in multiple diseases only in young or middle-aged people aged between 20 and 60 years). Notably, a subset of these taxa that were enriched in multiple diseases across all ages (the G1 group) was also associated with increased frailty in individuals in the ELDERMET cohort. These frailty marker taxa (all belonging to the unhealthy-associated pathobiont group) were also linked with detrimental metabolic functionalities such as the production of hydrophobic bile acids, ethanol, trimethylamine and para-cresol. Thus, although it is difficult to distinguish between causal and consequential microbiome changes, there are ‘usual suspects’ with functionalities that might contribute to a vicious cycle of progressive decline in health. Only a small proportion of the taxa-to-metabolic associations in our study could be verified by interrogating faecal and/or serum metabolomic data. However, as discussed later, these findings have been corroborated in several studies.
Table 4 presents other examples of microbial metabolites and macromolecules that have demonstrated activities upon host metabolism, inflammation and disease risk. Urolithins are an interesting class of gut microbiome-derived compounds that have been hypothesized to be potentially distinguishing markers between healthy young and aged (especially unhealthily aged) individuals. Urolithins are produced by gut microorganisms from dietary plant components, especially ellagic acid. Previous studies have shown that individuals can be divided into three groups, known as urolithin metabolotypes (UM), based on their urolithin patterns: UM-A, UM-B and UM-O. Although the prevalence of the health-associated UM-A metabotype was reported to decrease with age, UM-B, which is associated with colorectal cancer and metabolic syndrome, showed a progressive increase in prevalence with age. Notably, UM-B was characterized by increased levels of iso-urolithin A, whose production has been attributed to an unknown member of the pathobiont Eggerthellaceae family.

Cytolethal-distending toxin-producing Campylobacter strains, colibactin-producing Escherichia coli strains and Fusobacterium are other Group 2 pathobiont lineages (observed to be increased with age) that can induce colorectal carcinogenesis either by DNA-damaging toxins or hyper-inflammatory cell surface proteins, as shown primarily in cell and organoid systems and animal models. Pathobiont-mediated physiological decline in ageing might be driven not only by the production of detrimental metabolites but also by the consumption of beneficial metabolites. For example, Desulfovibrio can dissimilate SCFAs such as butyrate, a gut microbiome-derived metabolite that has been shown to have a multitude of properties to prevent age-linked physiological decline.

In apparently healthy older people, the loss of prominent butyrate producers belonging to Group 1, such as Faecalibacterium, Roseburia, Coprococcus and Eubacterium spp. (especially E. rectale), typically associated with health in younger individuals, is less severe. The benefits of prolonged retention of a ‘youth-like’ microbiota have been further shown in a large-scale mouse study where faecal microbiota transplantation (FMT) from young mice reversed ageing-linked deterioration in peripheral and brain immunity and attenuated selected age-associated impairments in cognitive behaviour in aged mice. Furthermore, studies on humans have observed that, in apparently healthy older people, the loss of Group 1 members is compensated for by the gain of alternate butyrate-producing Group 3 taxa such as Odoribacter, Butyricimonas, Butyrivibrio and Oscillospira (Tables 2, 3). Butyrate is a potentially pivotal inhibitor of unhealthy ageing by virtue of multiple properties that delay the ageing host from shifting towards physiological decline. These properties include preventing inflammation (by multiple means, including acting as an energy source for colonicocytes, improving barrier function and downregulating endocannabinoid-regulated adipogenesis), insulin-resistant inflammation.

**Fig. 2 | Physiological, social and disease-related influences on the microbiome of older people.** Progressive decline in physiological function along the alimentary tract changes the internal microenvironment in all individuals to a variable degree and indirectly affects nutrient intake by older people. Additional variables that shape the microbiome of older people include lifelong lifestyle choices, contact with the external microenvironment, social networks (the social microbiome), and the reciprocal influences of age-related diseases and their treatment.
pathobionts include one or more taxa belonging to the following lineages: C. difficile, Ruminococcus torques, Streptococcus, and other, multiple studies have associated the Group 3 member (especially the species Akkermansia muciniphila) with beneficial traits (some causally using preclinical studies), including facilitating the growth of butyrate producers (by producing acetate), which results in reduced loss of colonic bilayer (thereby reducing inflammation), reduced activation of B1a cells (thereby preventing insulin resistance), prevention of cellular senescence (tryptophan mediated as well as through modulation of bile acid profiles), ameliorating progeroid symptoms as well as markedly reducing resistance (by regulation of B1 cell activity), cancer onset (by acting as a histone deacetylase inhibitor and facilitating programmed cell death) and cognitive decline (by acting as a putative negative regulator of amyloidosis and neuro-inflammation)67,68. 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Table 3 | Targeted studies investigating gut microbiome alterations related to specific aspects of ageing-related health loss

| Aspect of unhealthy ageing | Study (cohort size) | Country/region | Molecular technique | Main alteration associated with condition investigated |
|----------------------------|---------------------|----------------|---------------------|-----------------------------------------------------|
| Frailty                    | Claesson et al.652   | Ireland        | 16S                 | Parabacteroides, Anaerotruncus, Coprobacillus increased; core SCFA producers and core gut microbiota decreased |
| Frailty                    | Ghosh et al.61 (189) | Ireland        | Shotgun             | Pathobionts with production capacity of multiple detrimental metabolites increased; SCFA producers decreased |
| Frailty                    | Jackson et al.517 (728) | United Kingdom | 16S                 | Pathobionts increased; SCFA producer Faecalibacterium prausnitzii decreased |
| Frailty                    | Lim et al.66 (176)  | Korea          | Shotgun             | Pathobionts increased; Prevotella copri, SCFA producer Coprococcus eutactus decreased |
| Frailty                    | Maffei et al.69 (~80) | United States  | 16S                 | Pathobionts, Ruminococcus, Coprococcus increased; alpha diversity decreased |
| Frailty                    | Zhang et al.302 (27) | China          | 16S                 | Ruminococcus torques, Atopobiiaceae increased; Gemella, Eubacterium ruminantium, Azospira decreased |
| Frailty                    | Picca et al.15 (35) | Italy          | 16S                 | Ruminococcus increased; Christensenellaceae, Barnesiellaceae reduced |
| Reduced physical activity  | Langsetmo et al.26 (373) | United States | 16S                 | Coprococcus, Eggerthella, Anaerotruncus, Megaphaera increased; Clostridium, Faecalibacterium, Lachnospiraceae, Prevotella decreased |
| Reduced physical activity  | Fart et al.1 (98)   | Sweden         | Shotgun             | Bilophila positive; Faecalibacterium prausnitzii decreased |
| Cardiometabolic disease    | Taniguchi et al.34 (33) | Japan         | 16S                 | Clostridioides difficile increased; Oscillospira decreased |
| Cognitive decline          | Verdi et al.177 (NA) | United Kingdom | 16S                 | Pathobionts, Ruminococcus, Lactobacillus, Blautia increased; Prevotella, Odoribacter, Christensenellaceae, Barnesiella, Butyrivibrio, Lachnospira, alpha diversity decreased |
| Cognitive decline          | Anderson et al.59 (37) | United States | 16S                 | Akkermansia and Lentinisphaerae decreased |
| Cognitive decline          | Manderino et al.65 (43) | United States | 16S                 | Akkermansia decreased |
| Parkinson disease          | Heinzl et al.17 (666) | Germany        | 16S                 | Pathobionts increased; Prevotella, core SCFA producers, Bifidobacterium, Odoribacter, Victivallis decreased |
| Alzheimer disease          | Haran et al.37 (108) | United States  | Shotgun             | Pathobionts increased; Butyrivibrio, core SCFA producers and Adlercreutzia equolifaciens decreased |
| Migraine                   | Chen et al.65 (108)  | United Kingdom | Shotgun             | Pathobionts increased; core SCFA producers, Butyrivibrio, Bifidobacterium adolescentis, other SCFA producers decreased |
| Reduced bone mass density  | Das et al.66 (181)   | Ireland        | 16S                 | Pathobionts, Lactobacillus increased |
| Reduced bone mass density  | Li et al.56 (102)    | China          | 16S                 | Roseburia, Bifidobacterium and Lactobacillus decreased |
| Visceral fat deposition     | Le Roy et al.63 (1,760) | United Kingdom | 16S                 | Pathobionts increased; Oscillospira, Christensenellaceae, Ruminococcaceae, Lachnospiraceae decreased |
| Obesity and metabolic syndrome | Zhong et al.62 (382) | Ireland        | 16S                 | Collinsella, Bifidobacterium, Paraprevotella increased; Akkermansia, Faecalibacterium, Prevotella decreased |
| Comorbidity                | Singh et al.64 (65)  | United States  | 16S                 | Pathobionts increased; Akkermansia decreased |
| Chronic kidney disease and frailty | Margiotta et al.65 (64) | Italy         | 16S                 | Pathobionts and Lactobacillus increased; Roseburia, Faecalibacterium and Prevotella decreased |
| Mortality (among centenarians) | Luan et al.51 (75) | Chinaa | Shotgun             | Akkermansia muciniphila, Alstipes sp., Bacteroides sp., Butyrivibrio catus, Prevotella stercora decreased |
| Progeria                   | Bárcena et al.67 (14) | Spain          | 16S                 | Akkermansia decreased |
| Comorbidities (among long-living individuals) | Zhang et al.101 (21) | China | Shotgun             | Pathobionts and xenobiotic degradation pathway genes increased |

Pathobionts include one or more taxa belonging to the following lineages: Desulfovibrio, Bilophila, Eggerthella, all Enterobacteriaceae, Campylobacter, Fusobacterium, Streptococcus, Anaerotruncus, Bacteroides fragilis, Campylobacter, Actinomyces, Corynebacterium, Staphylococcus, Parvimonas, Porphyromonas, Flavonifractor, Ruminococcus torques, R. gnavus, Clostridium asparagiforme, C. hathewayi, C. bolteae, C. citroniae, C. clostridioformae, C. symbiosum, C. hylemonae, C. scindens and C. difficile; core SCFA producers include members of the following genera: Faecalibacterium, Roseburia, Eubacterium, Dorea, Coprococcus and Blautia. NA, not available; SCFA, short-chain fatty acid. *Indicates that the cohort size does not include individuals <50 years of age. *Indicates that the study includes centenarians.
Positive association of *Akkermansia* in these diseases is a cause or an effect of a variable host-specific immune response\(^8\). Other Group 3 members, *Barnesiellaceae* and *Christensenellaceae*, have been associated with increased physical activity and are depleted in humans with sarcopenia, inflammation and mitochondrial DNA damage\(^9\). Strains belonging to the family *Odoribacteriaceae* (related to another Group 3 member *Odoribacter*) were shown to produce a novel bile acid called isovaloliticholic acid, which was enriched in the faecal metabolome of centenarians and showed antimicrobial effects on multidrug-resistant pathogens, including *Clostridioides difficile*\(^4\) (Fig. 4). Further evidence for the microbiome basis of longevity comes from a study in *Caenorhabditis elegans*, where screening a mutant bank of *E. coli* identified 12 microbial genes associated with longevity, including those linked to colanic acid secretion, which in turn beneficially regulate mitochondrial gene transcription and the unfolded protein response by facilitating transcription of mitochondrial chaperone genes\(^4\).

Despite generally consistent findings, ageing-linked microbiome alterations also exhibit variation across studies. One example is Roseburia. While ageing studies...
Inter-study variations
Variations in the patterns of gut microbiome alterations detected across different studies investigating the same (or similar) host trait or phenotype (for example, age, BMI, a disease or disorder, or specific dietary patterns).

Shotgun metagenomics
A method of community genomic profiling that involves the extraction and sequencing of the entire genomic content of all cells belonging to a given microbial community.

in Italian, Irish and Thai individuals have reported a statistically significant reduction of Roseburia spp. abundance with age, studies of Russian, Chinese and Korean populations have observed an increase in the relative abundance of opportunistic allochthonous bacteria (that is, those not normally replicating stably in the gut) along with an increase in the proportional abundance of pathogens and a decrease in commensals such as Streptococcus thermophilus. This finding appeared to be driven by loss of the core microbial taxa associated with healthy ageing.

In addition to the consistent taxonomic alterations observed in healthy individuals, studies investigating microbial determinants of healthy ageing stratify individuals on the basis of various indices of physiological well-being and frailty prior to selecting appropriate study populations. Furthermore, the observed microbial alterations will also depend on the index of unhealthy ageing used to stratify individuals. Nevertheless, despite inter-study differences, the patterns of microbial alterations discussed previously are of sufficient consistency to suggest biological relevance and a plausible basis for the design of microbiome-based interventions against unhealthy ageing.

In addition to the consistent taxonomic alterations summarized previously, a 2021 study (investigating two US-based population-level cohorts of 3,653 and 907 individuals) linked the degree of ‘uniqueness’ (a measure indicating how dissimilar an individual’s microbiome is from their nearest neighbour in the given population cohort) of the microbiome with ageing. This finding appeared to be driven by loss of the core genus Bacteroides and agrees with the taxonomic alterations associated with ageing discussed previously.
Prebiotic
Nutritional supplements designed to increase the abundance of specific target groups of beneficial microorganisms based on restricted catabolic ability in certain taxa

Symbiotics
Single or consortia of beneficial microorganisms that are administered in combination with probiotics

Postbiotics
Deliberately inactivated (heat-killed) microorganisms, cell components or microbiota-derived metabolites that confer health benefits

Quantitative polymerase chain reaction (qPCR). A method of real-time microbial quantification in a given sample that relies on measuring the change in PCR amplicon copy number (in this context, amplified by primers designed against a phylogenetic marker gene corresponding to a given species or a microbial group) during the cycles of the PCR; copy numbers of phylogenetic marker gene regions belonging to microbial lineages in higher abundance are expected to be amplified faster, resulting in a faster increase in the strength of fluorescent oligonucleotide probes targeted at these lineages.

Fluorescence in situ hybridization (FISH). A method of physically locating or enumerating the population of a specific microorganism or cell type by using fluorescent oligonucleotide probes that bind to specific genomic sequences in the target cells with high sequence complementarity; it can be used to measure either specific bacterial species or overall bacterial cell abundance (by using probes towards the universally conserved regions of the 16S rRNA gene).

(depletion of dominant Group 1 commensals compensated for by increased Group 3 commensals and Group 2 pathobionts). However, the link between uniqueness and healthy ageing is likely to be context dependent and additional studies are required to determine the validity of uniqueness as a marker of healthy and unhealthy ageing in different populations. More importantly, the enrichment or depletion of specific taxonomic lineages might be more valuable metrics of healthy ageing than summary statistics such as uniqueness or diversity.

Microbiome-based ageing interventions
Although functional versatility is a defining characteristic of the human gut microbiome, the responsiveness of the gut ecosystem to therapeutic modulation is unclear, particularly in older people, largely because the broader ecological effects of an intervention on core taxa have not been determined. Microbiome-directed or microbe-derived therapeutic interventions include prebiotic supplements (designed to increase the abundance of specific target groups of beneficial microorganisms), single or combined beneficial taxa alone or with a probiotic (symbiotics), postbiotics, or FMT and health-linked dietary regimens that can theoretically facilitate a broader shift in the gut microbiome towards health. The aim of such interventions is to break the self-perpetuating cycle of ageing-linked physiological decline facilitated by a disease-susceptible microbiome. From this perspective, we propose that the increased abundance of Group 2 taxa and the depletion of Group 1 and Group 3 (discussed previously) are analogous to ‘buttons’ that drive unhealthy ageing. Thus, resetting these buttons should be the key goal of any microbiome-associated therapeutic intervention targeted to healthy ageing. While numerous studies of variable size, quality and design have addressed the onset targeted to healthy ageing. While numerous studies of variable size, quality and design have addressed the onset

Microbiome-based interventions to promote healthy ageing in older people are a work in progress; selected key studies are presented in TABLE 5. Only five studies have a cohort size of >100 individuals\(^ {39,40,49}\); excluding an across-study meta-analysis\(^ {39}\), the mean cohort size of the other older people-focused interventions is only approximately 36 (this is excluding FMT intervention case studies involving either a single patient or less than 5 patients). In addition to the low sample size, many studies used low-resolution microbiome profiling, including quantitative polymerase chain reaction (qPCR) and fluorescence in situ hybridization (FISH)\(^ {48,113,114}\). The questions posed by intervention studies also vary, with some limited to effects on host physiology rather than associated microbiome alterations\(^ {39,49,113,114}\). Most studies in this list involving postbiotics and FMT have not performed any microbiome profiling and have relied on changes in host physiology and well-being (TABLE 5). Efficacy metrics have also varied from improvements in inflammatory status, insulin resistance, frailty and cognitive function to responsiveness to vaccines, which has been disappointing with regard to achieving superior vaccine response after microbial/prebiotic supplementation\(^ {39,49,113,114}\), but have shown promising results in the case of postbiotic interventions such as administration of heat-killed Lactobacilli\(^ {113,114}\). Encouraging reports of other postbiotics, such as using butyrate to treat inflammatory diseases (such as ulcerative colitis) in younger cohorts \((n = 216)\) and cognitive decline in mice models\(^ {113,114}\), remain to be assessed in older people. In addition, FMT in older people has largely been limited to the treatment of C. difficile infections\(^ {48,113,114}\). While promising, such strategies risk transmission of pathobionts or detrimental microbiota in the context of an older host\(^ {112,122}\). FMT for other age-associated disorders in older people has been limited to isolated case reports\(^ {39,113,114}\).

Notwithstanding these limitations, there are grounds for optimism for microbiome-targeted interventions, particularly in the context of unhealthy ageing. In pilot studies of polyphenol-rich foods, prebiotics and some probiotics that included sub-cohorts of older and younger individuals, efficacy was more pronounced in older people, especially in the unhealthy group with frailty, insulin resistance and obesity, than in healthy and younger individuals, particularly for polyphenol-based and prebiotic/oligosaccharide-based interventions\(^ {113,114}\). A popular but perhaps simplistic explanation for these effects emphasizes increased intestinal permeability in older people\(^ {113}\). Increased gut permeability is associated with inflammaging, frailty and insulin resistance\(^ {113,114}\). However, a polyphenol-based pilot intervention found that the age-linked beneficial effects included changes in the microbiome\(^ {113,114}\). The study investigated the effects of daily freeze-dried blueberry powder consumption for 6 weeks on the faecal microbiota of 17 women in two age groups (aged 21–39 years and 65–77 years, respectively). Specifically, consumption of blueberries (a source of polyphenols) was associated with increased microbiome alpha diversity and increased abundance of butyrate-producing Group 1 taxa \((Faecalibacterium\) and \(Coprooccus\)) and Group 3 taxa \((Butyrivimonas\) and \(Barnesiella\)), which was accompanied by increased antioxidant activity with respect to baseline compared with placebo controls.

Similar improvements in microbiome composition have also been reported for other interventions in older people \(\text{TABLE 5}\). The quality of evidence for ‘resetting’ microbiome alterations in unhealthy ageing varies with the type of intervention, duration and dosage. For example, for interventions with probiotics and prebiotics, the primary beneficial objective has been to increase the abundances of the putatively beneficial taxa (primarily \(Lactobacilli\) and \(Bifidobacteria\)) in addition to the butyrate producers \((\text{from Group 1 and Group 3}\); \(\text{fig. 3}\)) and \(\text{Akkermansia}\) \((\text{Group 3}\); \(\text{fig. 5}\)). These lineages not only have beneficial attributes, such as promoting insulin sensitivity and maintaining intestinal barrier integrity\(^ {113,114}\), but also cross-feed the butyrate producers by providing acetate\(^ {113}\). Additionally, lactobacilli facilitate butyrate uptake in colonocytes by induction of monocarboxylate transporter 1 (MCT1) as demonstrated in Caco-2 human colon cell lines (graphically summarized in \(\text{fig. 5}\))\(^ {113}\). Many prebiotic and probiotic studies
Table 5 | Intervention studies targeting the microbiome in older people

| Study                        | Duration and cohort size | Intervention type                        | Molecular technique* | Study aim or system targeted                                                                 | Effect on microbiome                                                                 | Physiological effects                                                                 |
|------------------------------|--------------------------|------------------------------------------|----------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Ghosh et al.                 | 1 year, 612              | Diet (Mediterranean diet)                | 16S                  | Inflammageing, cognitive function, disease incidence and frailty                               | Diversity, keystone taxa, Group 1 taxa, *Prevotella*, SCFA producers positive; Group 2 pathobionts negative | Improvements in all health measures associated with an intermediate microbiome response |
| Mitchell et al.              | 10 weeks, 28             | Diet (protein rich)                      | 16S                  | Generation of volatile toxic compounds                                                      | No significant changes                                                               | No significant changes                                                                 |
| Nappal et al.                | 6 weeks, 17              | Diet (Mediterranean diet plus keto diet) | 16S                  | Alzheimer disease                                                                          | Group 3 taxa, faecal butyrate, propionate positive                                   | Butyrate negatively associated with amyloid β-40/42, *Proteobacteria* positive        |
| Ntemiri et al.               | 6 weeks, 17              | Diet (blueberry intake)                  | 16S                  | Inflammation, insulin resistance, oxidative stress                                         | Group 1 and Group 3 taxaons positive                                                 | Antioxidant activity increased (only in older people)                                  |
| Igwe et al.                  | 8 weeks, 31              | Diet (QGP intake)                        | 16S                  | Cognition, inflammation                                                                    | No significant changes                                                               | No significant changes                                                                 |
| Del Bo et al.                | 8 weeks, 66              | Diet (PR diet)                           | 16S                  | Inflammation, insulin resistance, cardiometabolic health                                   | Group 1 and other SCFA producers increased                                           | Zonulin, blood pressure (in women) decreased; effects pronounced in individuals with higher baseline BMI and insulin resistance |
| Ostane et al.                | 8 weeks, 125             | Diet (nutraceutical supplementation)     | qPCR                 | Inflammation, insulin resistance                                                           | NA                                                                                 | Insulin resistance, inflammatory markers decreased                                     |
| Ruiz-Saavedra et al.         | NA, 73                   | Adherence scores to a healthy diet (scores) | 16S                  | Cognition, blood glucose and pressure                                                       | NA                                                                                 | All measures of blood pressure decreased (only in older people)                         |
| Zengul et al.                | NA, 29                   | Diet (dietary fibre)                     | 16S                  | Breast cancer                                                                               | Group 2 pathobionts decreased                                                        | Serum oestradiol decreased                                                             |
| Cancello et al.              | 4 weeks, 20              | Diet plus MS                             | 16S                  | Obesity, insulin resistance, inflammation                                                  | Group 3 and Group 1 members increased; Group 2 pathobionts decreased; effect was higher in individuals with obesity | Weight decreased, *Faecalibacterium* and Akkemansia negatively associated with obesity measures |
| Qu et al.                    | NA, 689                  | MS (meta-analysis)                       | NA                   | Inflammation                                                                               | NA                                                                                 | High variability; no significant association                                           |
| Buigues et al.               | 13 weeks, 50             | Prebiotics (inulin, FOS)                 | NA                   | Cognitive decline, frailty                                                                  | NA                                                                                 | Physical frailty measures decreased                                                    |
| Theou et al.                 | 13 weeks, 50             | Prebiotics (inulin, FOS)                 | NA                   | Frailty                                                                                    | NA                                                                                 | Reduction in frailty; effects pronounced in individuals who are frail                   |
| Tran et al.                  | 26 weeks, 37             | Prebiotics (consortia)                   | 16S                  | Inflammation                                                                               | Specific Group 1 members and *Parabacteroides* increased in individuals who are frail | Inflammatory CXCL11 decreased in individuals who are frail                              |
| Alfa et al.                  | 12 weeks, 84             | Prebiotics (amylose, amylpectin)         | 16S                  | Inflammation, insulin resistance                                                           | *Bifidobacterium, Prevotella, Group 2 taxa, butyrate, *Desulfovibrio* increased     | HOMA-IR reduced; effect pronounced in older people                                     |
| An et al.                    | 4 weeks, 48              | Prebiotics (SBP, maltodextrin)           | 16S                  | Generation of volatile toxic compounds                                                     | NA                                                                                 | NA                                                                                     |
| Chung et al.                 | 10 days, 21              | Prebiotics (AXOS, maltodextrin)          | 16S                  | SCFA and microbiome status                                                                  | *Bifidobacterium, Prevotella, Oscillibacter increased                                | Higher SCFA linked with higher *Prevotella*                                             |
| Study                        | Duration and cohort size | Intervention type | Molecular technique | Study aim or system targeted | Effect on microbiome | Physiological effects |
|-----------------------------|--------------------------|-------------------|---------------------|-----------------------------|----------------------|-----------------------|
| Watson et al.                | 5 weeks, 20              | Prebiotics (inulin) | 16S                 | Stool characteristics       | No significant changes| No significant changes |
| Birkeland et al.             | 6 weeks, 25              | Prebiotics (inulin) | 16S                 | SCFA and microbiome status  | *Bifidobacterium* adolescentis, Group 1, *Bacteroides ovatus* increased; *Ruminococcus* decreased | SCFA increased |
| Lebihuber et al.             | 4 weeks, 20              | MS (consortia)     | qPCR                | Alzheimer disease           | *Faecalibacterium* increased | Zonulin decreased; zonulin negatively correlated with CDT, MMSE |
| Gao et al.                  | NA, 33                   | MS (consortia)     | 16S                 | Inflammation                | *Blautia*, *Faecalibacterium*, Pathobionts increased | IL-1β decreased |
| Kim et al.                  | 12 weeks, 53             | MS (*Bifidobacteria*) | 16S                 | Brain function              | *Clostridiales*, *Eubacterium* increased | Serum BDNF decreased |
| Eloe-Fadrosh et al.         | 12 weeks, 12             | MS (*Lactobacilli*) | 16S, RNA sequencing | NA                          | Differential gene transcription | NA |
| Spaiser et al.              | 3 weeks, 32              | MS (consortia)     | 16S, qPCR           | Inflammation                | *Bifidobacterium*, *Faecalibacterium* increased; *Escherichia* decreased | Anti-inflammatory IL-10 increased |
| Nyangale et al.             | 4 weeks, 36              | MS (*Bacillus coagulans*) | FISH                | Inflammation                | *Faecalibacterium praunitzii* increased | Anti-inflammatory IL-10 increased and pro-inflammatory TNF increased |
| Sanborn et al.              | 13 weeks, 145            | MS (*Lactobacilli*) | NA                  | Cognitive decline           | NA                   | Improvements in multiple scores of cognitive function |
| Costabile et al.            | 3 weeks, 37              | MS (*Lactobacilli*) | 16S                 | Inflammation, cardiometabolic health | *Parabacteroides*, *Oscillospira*, *Desulfovibrio* increased | LDL/total cholesterol, C-reactive protein reduced |
| Björklund et al.            | 2 weeks, 47              | MS (*Lactobacilli*) plus prebiotic (lactitol) | qPCR | Gut microbiome alterations | Reduced loss of SCFA producers | NA |
| Nilsson et al.              | 1 year, 70               | MS (*Lactobacilli*) | NA                  | Bone loss                   | NA                   | Reduced loss of bone mineral density |
| Nyangale et al.             | 4 weeks, 6               | MS (*B. coagulans*) plus prebiotic (GOS/FOS) | FISH | Inflammation, SCFA status | Group 1 SCFA producers increased | Faecal SCFA increased |
| MacFarlane et al.           | 4 weeks, 43              | MS (*Bifidobacteria*) plus prebiotic (inulin) | FISH | Inflammation | *Actinobacteria* and *Firmicutes* increased; *Proteobacteria* decreased | SCFA increased; TNF decreased |
| Akatsu et al.               | 12 weeks, 15             | Postbiotic (heat-killed *Lactobacilli*) | NA | Influenza vaccine response | NA | Significant improvement in antibody titre for all three variants (H1N1, H3N2 and B) |
| Maruyama et al.             | 12 weeks, 45             | Postbiotic (heat-killed *Lactobacilli*) | NA | NA | Improved immunity | NA |
| Shinkai et al.              | 20 weeks, 300            | NA | Improved immunity | NA | Significantly reduced incidence of common cold |
| Kotani et al.               | 12 weeks, 80             | NA | Salivary IgA and mucosal immunity | NA | Improved IgA production and mucosal immunity |
| Andreux et al.              | 4 weeks, 60              | Postbiotic (urolithin A) | NA | Mitochondrial and cellular health | NA | Improved mitochondrial gene expression and fatty acid oxidation |
report beneficial effects on host physiology, such as reduction in insulin resistance, zonulin gene expression (a marker of barrier function), inflammation, and levels of brain-derived neurotrophic factor (BDNF), which is upregulated during neuro-inflammation. In addition, improved cognitive function and cardiometabolic health, previously associated with butyrate, have been reported\textsuperscript{106,111,113–115,130,132,141–144} (FIG. 3).

Akkermansia (Group 3; or the species A. muciniphila, specifically) is another hallmark of healthy ageing. Administration of live or pasteurized A. muciniphila for 3 months has been reported to reduce body weight, insulin resistance and levels of cardiometabolic risk factors in a Belgian cohort of 32 individuals ranging between 18 and 70 years of age\textsuperscript{85}. While prebiotics and probiotics have been consistently linked with beneficial Group 1 and Group 3 taxa, there are conflicting reports on their influence on the abundance of pathobionts (Group 2 taxa). A significant reduction in Proteobacteria\textsuperscript{10,113} should be weighed against a reported increase of pathobionts such as Desulfovibrio, Streptococcus and Enterococcus\textsuperscript{114,132,144}.

In contrast to supplements, whole diet-based interventions promise a fundamental resetting of gut microbiome composition\textsuperscript{104,105,130,147}. However, most studies have focused on the intake of specific dietary components, often in small studies of short duration (TABLE 5). To address this limitation, a multi-national European consortium conducted the first comprehensive older people-targeted NU-AGE Mediterranean Diet (MedDiet) intervention\textsuperscript{104}. The MedDiet regimen is characterized by increased intake of vegetables, fruits, legumes, fish, olive oil, and nuts and reduced consumption of red meat, dairy products and saturated fats. The MedDiet has been linked with reduced mortality and reduced onset of multiple chronic diseases and frailty\textsuperscript{106}. The study included 323 test individuals and 289 control individuals, all of whom were pre-frail individuals over age 65 years followed for 1 year. Adherence to the MedDiet for a 1-year intervention period was correlated with retention of microbiome composition compared with that of the control individuals who maintained their normal diet; the intervention arm individuals also retained higher levels of health metrics, including levels of pro-inflammatory and anti-inflammatory cytokines, cognitive function and physical frailty, and incidence of non-communicable diseases\textsuperscript{104}. The study provided the first clear evidence that a MedDiet can help to ‘reset’ the microbiome alterations that initiate the vicious cycle of unhealthy ageing-linked physiological decline (FIG. 5). Strict adherence to the diet was associated with retention of the keystone taxa (such as Faecalibacterium prausnitzii and Bacteroides thetaiotaomicron) constituting the core gut microbiome and with retention of microbiome diversity. The Group 1 butyrate producers, including Faecalibacterium prausnitzii, Roseburia hominis, E. rectale and Prevotella copri, were positively associated with MedDiet adherence. By contrast, pathobionts (the Group 2 taxa group), such as R. torques, Collinsella aerofaciens, Clostridium ramosum and Flavonifractor plautii, were negatively associated. Taxa that were negatively associated with the MedDiet had greater genomic coding capacity for producing potentially harmful metabolites such as deoxycholic acid, lithocholic acid and para-cresol, all of which are linked to unhealthy ageing (as described in FIG. 4).

To quantify the beneficial microbiome alterations associated with MedDiet intake, we computed MedDiet-associated microbiome scores, whereby higher scores were linked with physiological well-being (including negative associations with inflammatory markers and incidence of chronic diseases, colorectal cancer, and frailty and positive associations with cognitive scores). Thus, it seems that adherence to the MedDiet initiated specific changes in microbiome composition, resulting in an altered set of microbial metabolites promoting
improved host health, as previously hypothesized. The findings have been validated in several MedDiet intervention studies (not specifically focused on older people), which showed consistent enrichment of Faecalibacterium and Roseburia and depletion of pathobionts (such as R. torques and R. gnavus, Collinsella, members of...
pathobiont *Clostridium*, and *Flavonifractor plautii*), along with a decreased capacity for production of deoxycholic acid and lithocholic acid^{148–150} (fig. 5). These studies also highlighted the predictive value of the baseline gut microbiome for responsiveness to the MedDiet, with a higher abundance of *Prevotella copri* at baseline linked with less responsiveness for some health metrics (such as insulin sensitivity, reduced inflammation, and lower triglyceride and total cholesterol levels)^{148,149}. By contrast, other reports have observed a positive association between *Prevotella* abundance and lower cardio metabolic disease risk^{151,152}. Strain-level variations within this lineage probably account for these apparently contradictory results as observed previously for *Faecalibacterium prausnitzii*^{149}. Levels of the pathobiont *Collinsella* were also found to mediate the beneficial effect of dietary vegetable intake on lymphocyte counts^{153}.

In summary, beneficial responses to microbiome-based dietary interventions have been achieved, but transduction of dietary signals to the physiological homeostasis of the host can be highly personalized, depending on baseline microbiome composition^{152}. This observation calls for a better understanding of age-related deterioration in the microbiome and for precision in the selection of interventions matched for an individual's stage in that process of decline. Stages of microbiome deterioration associated with unhealthy ageing probably first include a reduction in the abundance of specific core or keystone species, followed by complete loss of the keystone members and surrounding community structure, enabling the outgrowth of pathobionts^{45,154} (fig. 6a). Simple dietary interventions are likely to fail or have limited efficacy in individuals whose diet-responsive keystone core species are low or already lost. Such scenarios will require combinatorial therapy involving diet adjustment supplemented by microbial restoration of keystone taxa at the central nodes of microbiome networks. Individuals with less microbiome deterioration might still be responsive to dietary interventions alone.
As previously noted for Prevotella, the host response to a given dietary intervention depends not only on the presence or absence of responsive taxa but also on the representation of specific strains of neutral taxa that are seemingly not related to the intervention. However, a variety of factors, including habitual diet, influence the baseline strain-level composition of the gut microbiome, which requires shotgun metagenomics for monitoring (fig. 6b). None of the microbiome-based interventions in older people to date has used this approach. Designing the near-perfect intervention would require elucidation of the interactions among host phenotype (physiology, demographics and lifestyle), the baseline gut microbiome, the intervention characteristics, and longitudinal responses in the microbiome and host physiology (fig. 6). Predictive models based on machine learning could be used to identify the factors driving the personalized response to diet as well as to dissect the interactions between the type of intervention, duration and dosage, the modulators (baseline host characteristics including diet and baseline microbiome composition), and the personalized response (at the level of the microbiome and host response). They can also be used to assess the translatability of these interactions across different sub-populations (fig. 6b).

Similar strategies have already been adopted in population-level studies of diet–microbiome–host
interactions in younger people, which predict cardiometabolic and post-prandial responses dependent on baseline host and microbiome characteristics. In addition, a shift from low-resolution methods, such as 16S profiling, to shotgun metagenomics will be essential for resolving species-specific and strain-specific variations. Thus, incorporating predictive strategies for the design of microbiome-based studies will help realize the promise of combining precision with preventive medicine for healthy ageing.

Conclusions and future projections

Microbiome science is maturing through a phase of wonderment to a stage where we know enough to know how much we do not know. The metric for true advances will be the clinical impact rather than technical or computational wizardry. However, convincing evidence for the efficacy of microbiome-based therapies in humans is sparse. Curiously, ageing might offer the greatest opportunities and prospects for success. The tenuous homeostasis and limited physiological reserve of some older people might mean that relatively small improvements in the microbiome can have a profound functional influence on the individual.

Although lifelong human studies of the microbiome are logistically complex, surrogate models of accelerated human ageing, such as progeria and Down syndrome, might be informative but are still works in progress. In addition, strain-level resolution in microbiome-based diagnostics and therapeutics is highly desirable but has not yet uniformly performed.

Translating knowledge of the microbiome for clinical benefit in older people will require answers to other lingering questions. Can the gut ecosystem of older people be ‘rewilded’ with missing or lost strains? What is the optimal way for restoring the microbiome? What are the dietary requirements for maintaining a restored microbiota? Will the food industry formulate new products informed by microbiome science as well as age-related physiology? Of course, delayed onset or outright prevention of unhealthy ageing and microbiome decline is preferable to therapeutic intervention. However, people will not return to ancestral or other diets simply because microbiome scientists think they are good for one’s ecosystem!

Better public health messaging and food policies will be required, supported by an unassailable evidence base. Moreover, the social determinants of health will always trump personalized predictors of response. Eating healthily is unaffordable for many. This fact has been shown in the United Kingdom, one of the most affluent countries/regions on the globe, where families in the lowest decile for household income would have to spend almost three-quarters of disposable income on food if they were to comply with national dietary guidelines, whereas the comparable figure for the wealthiest decile is only 6%. Dietary and other microbiome-based strategies for healthy ageing should be weighed against such social inequity and should seek to develop realistic solutions.

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Author contributions
All authors contributed equally to all aspects of the manuscript.

Competing interests
F.S. is a co-founder of three campus companies: Alimentary Health Ltd, Tucana Health Ltd (now named 4D Pharma Cork) and Atlantia Food Clinical Trials. P.W.O.T. is a co-founder of 4D Pharma Cork. T.S.G. declares no competing interests.

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