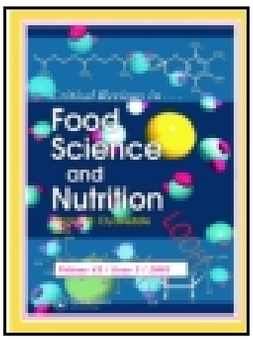

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

Gut microbiota and aging

Zongxin Ling, Xia Liu, Yiwen Cheng, Xiumei Yan & Shaochang Wu

To cite this article: Zongxin Ling, Xia Liu, Yiwen Cheng, Xiumei Yan & Shaochang Wu (2020): Gut microbiota and aging, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2020.1867054

To link to this article: https://doi.org/10.1080/10408398.2020.1867054

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2020.1867054

Taylor & Francis
Taylor & Francis Group

REVIEW

Gut microbiota and aging

Zongxin Ling[a]*, Xia Liu[b]*, Yiwen Cheng[a], Xiumei Yan[c], and Shaochang Wu[a#]

[a]Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China; [b]Department of Intensive Care Unit, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China; [c]Department of Geriatrics, Lishui Second People's Hospital, Lishui, Zhejiang, China

ABSTRACT

Aging is characterized by the functional decline of tissues and organs and increased risk of aging-associated disorders, which pose major societal challenges and are a public health priority. Despite extensive human genetics studies, limited progress has been made linking genetics with aging. There is a growing realization that the altered assembly, structure and dynamics of the gut microbiota actively participate in the aging process. Age-related microbial dysbiosis is involved in reshaping immune responses during aging, which manifest as immunosenescence (insufficiency) and inflammaging (over-reaction) that accompany many age-associated enteric and extraenteric diseases. The gut microbiota can be regulated, suggesting a potential target for aging interventions. This review summarizes recent findings on the physiological succession of gut microbiota across the life-cycle, the roles and mechanisms of gut microbiota in healthy aging, alterations of gut microbiota and aging-associated diseases, and the gut microbiota-targeted anti-aging strategies.

KEYWORDS

Aging; bacterial diversity; fecal microbiota transplantation; gut microbiota; life-span; succession

Introduction

Since 2000, the large aging population has become a major public health issue in China. The elderly population in China is growing exponentially, and this growth will last for decades. Elderly citizens in China currently account for 18.1% of the population, reaching 254 million, exceeding the summed population of Japan and Germany, and by 2050 nearly 35% will be age 60 or older (Fang et al. 2015). Such a sizable elderly population will impact the social and economic development of China. Physiological function decline seriously threatens the physical and mental health of the elderly population and is associated with a surge in the prevalence and incidence of age-associated diseases. It has become a research hotspot to investigate the aging mechanism, explore novel methods to delay aging, and improve the lifespan and quality of life of the aging population. The prevention of aging-associated diseases, improvement of elderly functions, maintenance of health status, and extension of healthy lifespan have become the new demands of the people under the current new situation in China. Realizing the active health of the aging population has become one of the key parts of the "Healthy China" project.

Traditionally, the human lifespan was thought to be determined by the combined influence of genetic, epigenetic, and environmental factors including life-style-associated factors such as exercise or diet (Dato et al. 2017; Smith et al. 2017), and the role of symbiotic microorganisms has been ignored. Microbes residing in a human gut are known as the "gut microbiota" and co-evolve with age. From birth, the gut microbiota drives maturation of the immune response, thereby contributing to homeostasis. Human and animal studies have reported microbial shifts in the aging gut under healthy conditions (Fahlstrom, Yu, and Ulfhake 2011; Langille et al. 2014; Vemuri et al. 2018; Dejong, Surette, and Bowdish 2020), which lead to increased intestinal inflammation and changes in host metabolism. As proposed by Nobel prize winner Elie Metchnikoff in 1907, aging is due to the poisoning of the body by the products of certain members of the human gut microbiota, and manipulation of the intestinal microbiota could extend lifespan. In recent years, the crucial role of the gut microbiota in human aging has attracted wide attention and considerable research. Accumulating evidence indicates that the gut microbiota plays vital roles in human development, physiology, immunity, and nutrition, so it is often referred to as the "forgotten organ" (O'hara and Shanahan 2006). The gut microbiota is a key factor in maintaining host homeostasis, and imbalances can lead to diseases. Although it is at the crossroad among nutrition, infection, immunity, and metabolism (O'hara and

CONTACT Zongxin Ling lingzongxin@zju.edu.cn State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, 310003, China; Shaochang Wu shaochang_wu@163.com Lishui Second People's Hospital, Lishui, Zhejiang, 323000, China.
*These authors contribute equally to this work.
#Present address: Department of Geriatrics, Lishui Second People's Hospital, Lishui, Zhejiang, China.
This article has been corrected with minor changes. These changes do not impact the academic content of the article.

Shanahan 2006), the gut microbiota has not received sufficient attention as a possible regulator of lifespan. Driven by the advent of modern sequence-based techniques such as metagenomics, the impact of the gut microbiota on human aging has become a transforming topic in microbiology research. The pathophysiological changes of the human gut microbiota during aging can cause immunosenescence and inflammaging, thereby accelerating or aggravating aging-related neurodegenerative diseases, metabolic syndrome, infection susceptibility, and other conditions that ultimately affect the quality of life of the aging population. Although the aging process is universal, progressive, gradual, and inexorable, human gut microbiota-targeted aging management is a novel approach in promoting health and anti-aging, effectively modulating the human gut microbiota has become a novel way to ensure active health for the aging population.

This review summarizes recent findings on the physiological succession of the gut microbiota across the life cycle, the roles and mechanisms of the gut microbiota on healthy aging, gut microbiota alterations and aging-associated diseases, as well as gut microbiota-targeted anti-aging strategies.

The physiologic succession of gut microbiota across the life cycle

The human body contains 10^{13} human cells and 10^{14} commensal microbiota, and the integrity of this superorganism is pivotal for health. In humans, the gut microbiota is dynamic over a lifetime, and the establishment of the stable gut microbiota undergoes progressive age-related physiological succession of species (Kim et al. 2011) driven by both internal host properties and external factors (Mateos et al. 2018). Physiological succession is defined as the somewhat orderly and predictable manner by which microbiota changes over time following host or habitat alterations. In the past, it was difficult to study microbial succession because communities are often diverse, and the ecological roles of microbes are typically poorly known. However, multi-omics techniques are now available that allow microbial communities and habitats to be surveyed across time at unprecedented levels of detail (Hamady et al. 2008). This dynamic gut microbial population develops rapidly from birth (initial exposure), changes rapidly before 3 years of age especially during the weaning period (transitional phase), then establishes adult-like stable microbiota (stable phase) until changes occur with aging (retrogression). The detailed developmental trajectory of gut microbiota over the human lifespan will help clarify the roles and mechanisms of microbes in host health and disease (Figure 1).

Initial exposure

Initial gut colonization in humans occurs at the very earliest stages of life, long before the newborn acquires its own microbiota. The maternal microbiota has been considered as the main contributor to the initial microbial seeding. Increasing evidence has confirmed the existence of a microbiota continuum between the mother and fetus, with maternal-fetal transmission of microbiota occurring during pregnancy (Selma-Royo et al. 2020). The assumption of in utero sterility has been challenged with the development of sequencing techniques, and intrauterine microbes from the placenta, amniotic fluid, endometrium, fetal membranes, umbilical cord, and meconium have recently been characterized (Dominguez-Bello et al. 2010; Ardissone et al. 2014; Zheng et al. 2015; Collado et al. 2016; Shi et al. 2018; Tapiainen et al. 2018; Stinson et al. 2019; Moreno et al. 2020; Pipan et al. 2020). The presence of intrauterine commensal microbes may initiate colonization within the fetus, and bacterial transmission through the placental barrier is a part of the normal developmental process. These bacteria have beneficial interactions with the active maternal immune system, leading to an immune-tolerant state and preventing fetal rejection (Escobar, Hincapie, and Barona 2020).

Besides intrauterine exposure, the initial process of gut microbiota colonization is also determined by factors such as mode of delivery, gestational age, feeding type, antibiotic exposure, and the surrounding environment, which have been discussed in other reviews (Ganal-Vonarburg, Hornef, and Macpherson 2020; Vandenplas et al. 2020). Delivery mode is generally accepted as a major factor that determines the initial colonization. The gut microbiota of vaginally delivered newborns is similar to that of the vaginal and gut microbiota of their mother (dominantly composed of *Lactobacilli*, *Bifidobacterium*, and *Prevotella*), whereas the gut microbiota of infants born by cesarean section (C-section) resembles the maternal skin and oral microbiota, which is dominated by *Streptococcus*, *Staphylococcus*, and *Propionibacterium* (Dominguez-Bello et al. 2010; Liu, Qin, et al. 2019). The different initial exposure may be attributable to the potential sources of pioneering bacteria. Undoubtedly, establishment of the gut microbiota is delayed in infants born by C-section during the postnatal period, which is a critical developmental window for immune system maturation (Olszak et al. 2012; Magne et al. 2017). Dominguez-Bello et al. conducted a pilot study in which infants delivered by C-section were exposed to maternal vaginal fluids at birth (Dominguez-Bello et al. 2016). Interestingly, the gut microbiota from these C-section-delivered newborn were similar to those of vaginally delivered ones. This has led to the increasingly popular clinical practice of "vaginal seeding," which is the iatrogenic transfer of vaginal microbiota to the C-section-delivered neonate to promote establishment of a "normal" newborn microbiota.

Gestational age at birth is another strong influencer of early gut microbiota structure following birth (Hill et al. 2017). Preterm neonates experience a number of unique challenges to microbiota establishment. The microbiota composition of preterm infants (<37 weeks of gestation) is different from full-term counterparts. Hesla et al. found that the gut microbiota of preterm infants contained a significantly greater abundance of Proteobacteria, while full-term infants harbor initially high relative proportions of Firmicutes and Actinobacteria at week 1 (Hesla et al. 2014). It was previously suggested that post-conceptional age, rather than postnatal age, is the main determinant of the bacterial community profiles in preterm infants (La Rosa

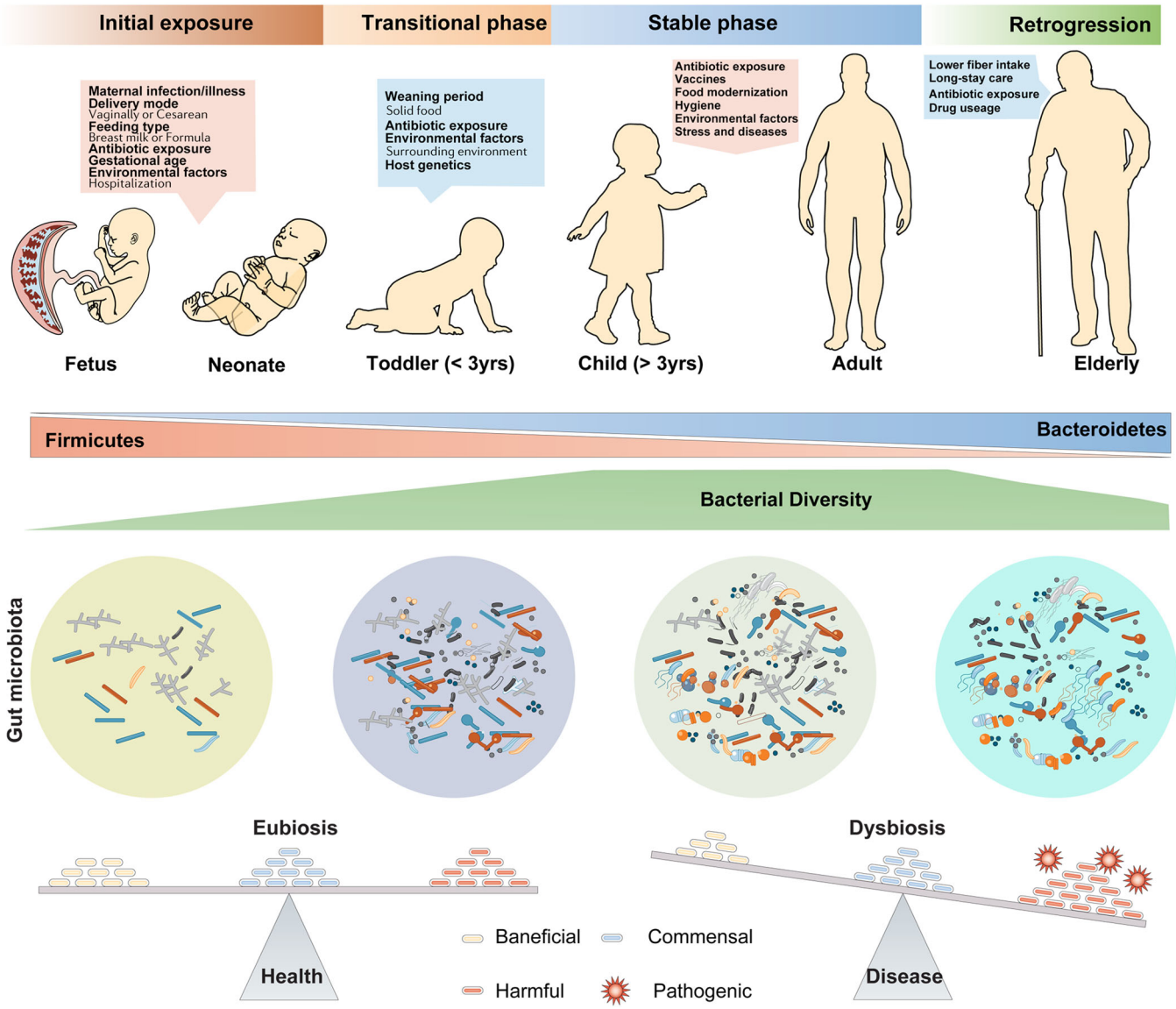

Figure 1. The physiologic succession of gut microbiota across the life cycle.

et al. 2014). With respect to postnatal age, Korpela et al. has reported that microbiota development proceeds in four phases indicated by the dominance of *Staphylococcus*, *Enterococcus*, *Enterobacter*, and finally *Bifidobacterium* (Korpela et al. 2018), while the *Enterococcus* phase was only observed among the extremely premature infants and appeared to delay microbiota succession. In fact, many challenges unique to preterm infants, such as C-section delivery, maternal and neonatal exposure to antibiotics, and the sterile environment of the neonatal intensive care unit may contribute to alterations in the natural acquisition pattern of gut microbiota.

Antibiotic exposure near the time of birth rapidly reduces the diversity and richness of the maternal gut microbiota, which limits transfer of maternal microbes to the neonate (Gibson et al. 2016). Maternal and infant exposure to antibiotics, especially intrapartum prophylaxis, affects the early life microbiota establishment in C-section delivered and preterm newborns (Forsgren et al. 2017). The influence of antibiotic use on the microbiota is greater than that of the gestational age (Zhou et al. 2020). Bokulich et al. showed that antibiotic exposure during the prenatal, perinatal, and postnatal periods was associated with a delay in microbial maturation from 6 to 12 months after birth (Bokulich et al. 2016). Arboleya et al. observed the higher levels of Firmicutes and the lower levels of Proteobacteria in antibiotic-free babies compared to infants whose mothers received antibiotics (Arboleya et al. 2016). It was hypothesized that the lower presence of *Bifidobacterium* and *Bacteroides* and the abundance of *Clostridium* and *Lactobacillus* in infants delivered by C-section are due to perinatal antibiotics administration (Rutayisire et al. 2016), which contributes to concomitant alterations in levels of intestinal short chain fatty acids (SCFAs) (Arboleya et al. 2016). Azad et al. determined that intrapartum antibiotics are associated with gut dysbiosis both in C-section and vaginal deliveries, although breastfeeding modifies some of these effects (Azad et al. 2013). In addition, antibiotic treatment of neonatal and pediatric populations can cause long-term enrichment of antibiotic resistance genes in the gut microbiota and promotes gene transfer to pathogens (Gibson, Crofts, and Dantas 2015).

Feeding is another important factor that influences intestinal colonization. Breast milk facilitates the most balanced microbiota development for infants, mainly because of its high content of unique oligosaccharides. Human milk oligosaccharides and glycoproteins can promote the growth of beneficial microorganisms, including *Bifidobacterium* (Bode 2012; Cong et al. 2016) and *Bacteroidetes*, but not pathogenic bacteria such as Enterobacteriaceae (Cong et al. 2016), which is important during the neonatal period in activating immunologic functions such as oral tolerance (Barnes and Powrie 2011). Beyond its nutritional benefits, the breast milk microbiota is the main direct postnatal source of bacteria such as *Bifidobacterium* for the infant's intestine, and these microbiota components can be vertically transmitted from mothers to infants during breastfeeding (Benítez-Páez et al. 2020). Ku et al. observed great differences of the gut microbiota among exclusively breastfed and formula-fed infants, with increased *Bifidobacterium* and decreased *Klebsiella* and *Serratia* in the breast milk-fed group (Ku, Kim, and Lee 2020). Lactation stage, gestational age, delivery mode, mother's diet and antibiotic exposure all influence the bacterial composition of breast milk. Mother-derived secretory immunoglobulin A in breast milk has been reported to shape the composition of the intestinal microbiota in neonatal mice at the age of weaning (Rogier et al. 2014). Dysbiosis of early gut colonization observed in infants born by C-section delivery may be aggravated by the aberrant breast milk microbiota (Hermansson et al. 2019), while prolonging exclusive breastfeeding was shown to benefit microbiota restoration (Ho et al. 2018; Liu, Qin, et al. 2019).

Besides the aforementioned factors, the surrounding environmental factors, hospitalization duration, birth weight, gender, genetic factors, race/ethnicity, maternal education and maternal diseases, will also impact initial colonization of the gut microbiota (Xu et al. 2020). Understanding this process in the human gut during childhood may help in the development of strategies to guide the formation of a health-promoting microbiota that could be maintained throughout the life of the host.

Transitional phase

The most dramatic compositional changes in the intestinal microbiota take place during weaning. The gradual switch from a diet composed exclusively of milk to a diet that includes other foods is a special and critical event for infants, but it is also a challenge to host gut physiology (Lalles et al. 2007). The introduction of solid food leads to a new phase in gut microbiota development that is characterized by a large increase in bacterial numbers and evolution toward a composition that looks more like the adult microbiota (Subramanian et al. 2014). A longitudinal study conducted by Magne et al. to explore gut microbiota changes through the weaning period revealed decreased interindividual variability in the dominant microbiota after cessation of breastfeeding (Magne et al. 2006). Due to the complementary introduction of a variety of novel food substances and nutrients, several studies found that alpha bacterial diversity increases during weaning, resulting in the replacement of Proteobacteria and Actinobacteria by Firmicutes and Bacteroidetes phyla as the dominant members of the infant microbiota (Fallani et al. 2011; Koenig et al. 2011). During the transition from the infant to the toddler stage, numerous studies reported that *Lachnospiraceae*, *Ruminococcaceae*, *Eubacteriaceae*, *Rikenellaceae*, or *Sutterellaceae* are enriched in infants with complementary feeding at age 9–18 months, while *Bifidobacteriaceae*, *Actinomycetaceae*, *Veillonellaceae*, *Enterobacteriaceae*, *Lactobacillaceae*, *Enterococcaceae*, *Clostridiales incertae sedis* XI, *Carnobacteriaceae*, and *Fusobacteriaceae* decreased (Avershina et al. 2014; Valles et al. 2014; Backhed et al. 2015; Laursen et al. 2016; Yang et al. 2020). These differences in the toddler gut microbiota may be attributed to the introduction of different food ingredients during the weaning period (Laursen et al. 2016). Specifically, intake of meats, cheeses, and Danish rye bread that are rich in protein and fiber are associated with increased α-diversity. Increased protein intake is correlated with enrichment of the Lachnospiraceae family and a decrease in saccharolytic bacteria such as members of the Bifidobacteriaceae family, while fiber ingestion is associated with higher levels of Prevotellacea (Laursen et al. 2016). In addition, Yassour et al. found that *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*, which are either absent or present at very low levels during early infancy, increase in abundance to adult levels at 12 months and 24 months, respectively (Yassour et al. 2016), and these changes correlated with increased carbohydrate intake in the weaning period. A recent clinical study of Indonesian children found that the fecal microbiota contains mainly *Bacteroides* and *Bifidobacterium* before weaning, which were found in low abundance in samples from the mothers. Interestingly, the fecal microbiome of children was mainly of the *Prevotella* type, with decreasing levels of *Bifidobacterium* after weaning, thus becoming more like the maternal fecal microbiome (Khine et al. 2020). The fecal *Bifidobacterium* in children inversely correlated with the consumption of complex carbohydrates and fruits after weaning (Khine et al. 2020). Moreover, the timing of complementary feeding (3 and 12 months) influences not only gut microbiota diversity and composition, but also SCFAs concentrations over the first year of life, with *Bilophila* and *Roseburia* increasing during early complementary feeding (Differding et al. 2020). Wang et al. observed that dietary intake of high amylose maize starch resulted in significant alterations in the fecal microbial community in the weaning group, with significant increases in levels of *Prevotella*, *Veillonella*, and *Collinsella* associated with propionate production (Wang, Mortimer, et al. 2019). The weaning period is also characterized by important changes in the intestinal immune system. Many previous studies observed that perturbation of the gut microbiota during weaning leads to the disruption of immune homeostasis later in life (Prioult and Nagler-Anderson 2005; Gollwitzer and Marsland 2015; Gensollen et al. 2016). The specific cytokines related to immune cell proliferation and maturation increase, while decreasing levels of primary bile acids and increases in secondary bile acids are observed after weaning (Khine et al. 2020). Al Nabhani et al. found that the expanding microbiota at

weaning induces a vigorous immune reaction they termed a "weaning reaction"- that is programmed in time. Inhibition of the weaning reaction leads to pathological imprinting and increases susceptibility to colitis, allergic inflammation, and cancer later in life (Al Nabhani et al. 2019). Prevention of this pathological imprinting is associated with the generation of RORγt^{+} regulatory T cells, which require bacterial and dietary metabolites such as SCFAs and retinoic acid (Khine et al. 2020). Thus, the early life weaning period is associated with dramatic fluctuation of gut microbiota and corresponding alterations in immune responses, which can be considered a critical window of opportunity for microbial manipulation, due to the relatively unstable configuration of the incompletely developed gut microbiota.

Stable phase

After initial exposure and critical transitional windows within 3 years after birth, it is generally agreed that the human gut microbiota develops into the typical adult structure and composition that is relatively stable in adults (Rajilic-Stojanovic et al. 2009; Caporaso et al. 2011; Wu et al. 2011). However, a recent study suggested that microbiota development into the stable phase may take longer (Derrien, Alvarez, and De Vos 2019). The stable adult-type microbiota is characterized by higher bacterial diversity and a predominance of Firmicutes and Bacteroidetes (Ho et al. 2018). Unlike the previous two stages dominated by *Bifidobacterium*, *Bacteroides* and *Eubacterium* are the most common bacterial taxa in the gut microbiota of adults and are defined as core microbiome of the adult-type gut microbiota. Though these genera may be part of the normal gut bacterial community, the increased abundance of gut *Bacteroides* has been associated with higher body mass index in young children and *Veillonella* can be associated with different types of infection (Brook 1996; Schwiertz, Le Blay, and Blaut 2000; Vael et al. 2011; Lagier et al. 2012). However, the Human Microbiome Project revealed that various factors such as food modernization, vaccines, antibiotics, and taking extreme hygiene measures will reduce human exposure to microbial symbionts and led to shrinkage of the core microbiome, while the reduction in microbiome biodiversity can compromise the human immune system and predispose individuals to several modern diseases. According to the core microbiome, the adult-type gut microbiota can be divided into three clusters that are referred to as enterotypes: *Bacteroides*, *Prevotella*, and *Ruminococcus* (Arumugam et al. 2011; Costea et al. 2018). These three enterotypes represent multiple stable states in the human gut microbiota, and each is generally resilient. Certain perturbations such as antibiotics, probiotics, and diet shifts will temporarily disturb the gut microbiota; however, the resilience of the adult gut microbiota can overcome these environmental changes and maintain the original stable state or an alternative stable state. Maintaining a beneficial microbiota requires a homeostatic equilibrium within microbial communities, as well as between microorganisms and the host's intestinal interface. The resilience of the healthy microbiota protects us from dysbiosis-related diseases. Beyond the limits of gut microbiota resilience, transition from the original stable state into an alternative stable state can propel the host into a pre-disease state, making them more susceptible to the development of chronic diseases (Goyal, Dubinkina, and Maslov 2018), which suggests that gut microbial resilience has a key role in health and disease (Sommer et al. 2017). Omics studies comparing gut microbiomes and their interaction with, susceptible and tolerant hosts can detect markers of resilience. The neutralization or inhibition of disease drivers, together with the identification and promotion of health-promoting species and functions, can enhance gut microbiome resilience and lead to new disease-prevention strategies (Rosier, Marsh, and Mira 2018). Previous studies reported that the effects of dietary interventions with significant compositional changes can occur within 4 days and can cause an enterotype shift (Wu et al. 2011; Kovatcheva-Datchary et al. 2015). However, after about 10 days, enterotypes appeared to be stable (Wu et al. 2011), suggesting a tendency to recover to the original state. Of course, differences in taxonomic composition suggest that enterotypes may differ in functional and ecological properties. Zhong et al. demonstrated that correlations between dietary lifestyle and metabolic phenotypes exhibited striking enterotype dependency (Zhong et al. 2019). Morrison et al. showed that reducing soluble fiber can influence the synthesis of microbial metabolites that are important for regulating metabolic, immune, behavioral, and neurobiological outcomes (Morrison et al. 2020). Therefore, a healthy, stable state of the gut microbiota is a key link with host health, while the transition of the stable states are associated with adverse consequences later.

Retrogression

Aging is a major intrinsic factor that influences the makeup and activity of the gut microbiota. Lower fiber intake, long-stay residential care, non-steroidal anti-inflammatory drugs, and antibiotic use may be predisposing factors for this changes (O'toole and Jeffery 2015). Many studies found that age-related changes in the gut microbiota composition include decreased species diversity, increased inter-individual variations, higher levels of Proteobacteria, and lower levels of beneficial bacteria such as *Bifidobacterium*, and these changes may be associated with increased susceptibility to pathogen infection and gut mucosal barrier disturbance (Lahtinen et al. 2009; Claesson et al. 2012). Most noticeably, the characteristics of the microbiota in elderly subjects include alterations in the relative proportions of the Firmicutes and the Bacteroidetes. The elderly have a higher proportion of Bacteroidetes while young adults have higher proportions of Firmicutes, so the decreased ratios of Firmicutes/Bacteroidetes is one aging indicator (Mariat et al. 2009). The diversity-associated taxa comprising *Prevotella* and associated genera are affected the most by aging, with their abundance declining rapidly once individuals enter long-term care (Claesson et al. 2012). Claesson et al. found that the core microbiota of elderly subjects is distinct from

that previously established for younger adults in the ELDERMET cohort, with a greater proportion of *Bacteroides* and distinct abundance patterns of *Clostridium* groups (Claesson et al. 2011). Recent studies also observed that aging is characterized by an increasing abundance of subdominant species, as well as a rearrangement in their co-occurrence network (Biagi et al. 2016; Rampelli et al. 2020). The gut microbiota in healthy elderly showed an enrichment and/or higher prevalence of health-associated groups such as *Akkermansia*, *Bifidobacterium*, and Christensenellaceae (Biagi et al. 2016). Centenarians are a model for healthy aging because they have reached the extreme limit of life by escaping, surviving, or delaying chronic diseases. These oldest old have a microbiota that differs from older adults (Biagi et al. 2010), consistent with general age-related microbiota trends. One Chinese group use metagenomics to assess the changing patterns of the gut microbiota in centenarians during their transition from healthy status to death (Luan et al. 2020). *Faecalibacterium prausnitzii*, one species with anti-inflammatory properties, was markedly decreased in the centenarians' microbiota, while *Eubacterium limosum* was increased by more than ten-fold (Biagi et al. 2010). *Akkermansia muciniphila* is commonly considered an indicator of a healthy gut community and is significantly increased in the centenarian gut communities compared to other age groups (Biagi et al. 2010). Chinese researchers have also observed that four bacterial strains including two *Bacteroides* strains, one Ruminococcaceae strain, and one *Desulfovibrio* were correlated with both age and living region of the healthy elderly in Bama (Zhao et al. 2011). According to PiCRUSt functional inference, the gut microbiota of centenarians (aged 99 to 104 years) and semi-supercentenarians (aged 105 to 109 years) is more suited for xenobiotic degradation and shows a rearrangement in metabolic pathways related to carbohydrate, amino acid, and lipid metabolism. Changes in these bacterial populations and their corresponding functions represent the loss of health and youth-associated microbiota components and gain of an elderly associated microbiota, which can trigger the innate immune response (immunosenescence) and chronic low-grade inflammation (inflammaging) (Franceschi et al. 2007), leading to many age-related degenerative pathologies and unhealthy aging (Kim and Jazwinski 2018). This may explain the potential impact of the gut microbiota on health and aging.

The roles and mechanisms of gut microbiota during healthy aging

Healthy aging, a combination of old age and health, is often defined as freedom from specific disorders or desirable performance levels on functional tests (Brooks-Wilson 2013). Given the dramatically increased human lifespan, there is a growing emphasis to monitor healthspan in addition to lifespan in determining the effect of a manipulation on aging. In fact, lifespan and healthspan are intimately related, and individuals who live exceptionally long also tend to be healthy for much of their lives. Stroke, cardiovascular diseases, cancers and infections have become the leading causes of death in the elderly. Delay in the development of these diseases and postponement of cognitive and physical decline during healthy aging also reduces morbidity (Fries 1980). Generally, it is believed that human healthspan is determined by complex interactions among genetic, epigenetic, and environmental (primarily dietary and lifestyle) factors (Brooks-Wilson 2013; Govindaraju, Atzmon, and Barzilai 2015; Passarino, De Rango, and Montesanto 2016). Mounting evidence suggests that the gut microbiota plays vital roles in regulating healthy aging and ultimately impacts host lifespan. Galkin and his colleagues developed an accurate aging clock based on gut metagenomics using a cross-study dataset and deep learning, which achieved a mean absolute error of 5.91 years when tested on external data (Galkin et al. 2020). They found that keystone members of the gut community such as *Bacteroides*, *Eubacterium*, and *Bifidobacterium* have the greatest effect on age prediction and can be considered as potential aging biomarkers (Galkin et al. 2020). In addition, Biagi et al. proposed *Akkermansia muciniphila* as a likely candidate for a healthy aging biomarker (Biagi et al. 2016). A recent animal study confirmed that *Akkermansia muciniphila* is sufficient to exert beneficial effects to enhance healthspan and lifespan in mouse models, possibly due to its beneficial effect of reestablishing a healthy gut microbiota (Barcena et al. 2019). Dehoux et al. also found that butyrate-producing bacteria, akin to *Akkermansia muciniphila* or *Bifidobacterium*, can be an aging-related group and affect or be affected by the aging processes (Dehoux et al. 2016). The presence of microbiomic clocks in the human body makes the noninvasive, accurate lifespan prediction possible. Correction of accelerated aging-associated gut dysbiosis is beneficial, suggesting a link between aging and the gut microbiota that provides a rationale for microbiota-targeted interventions against age-related diseases.

As mentioned above, age-associated alterations in the composition, diversity, and functional features of the gut microbiota are closely correlated with an age-related decline in immune system functioning (immunosenescence) and low-grade chronic inflammation (inflammaging), and these changes might be the pathophysiological bases of many aging-related diseases. Inflammaging, one of the seven evolutionarily conserved mechanistic pillars of aging, is the long-term result of chronic physiological stimulation of the innate immune system and is characterized by an imbalance between pro- and anti-inflammatory responses during aging (Franceschi et al. 2000). Inflammaging plays an increasingly important role in the rate of aging and the development of age-related diseases. The gut microbiota has a central role in inflammaging, as it can release inflammatory products, and contribute to circadian rhythms and crosstalk with other organs and systems (Franceschi et al. 2018). The gut microbiota transforms environmental signals and dietary molecules into signaling metabolites to communicate with different organs and tissues in the host, mediating meal-related inflammation. Increased levels of inflammatory cytokines such as interleukin (IL)-6, IL-8 and tumor necrosis

factor α (TNF-α) are also correlated with age. Systemic TNF-α levels steadily increase during the lifespan, reaching high concentrations in aged individuals (Bauernfeind et al. 2016), and may be stimulated with increased bacterial components from the gut microbiota (Thevaranjan et al. 2017). Interestingly, Fransen et al. found that decreased *Akkermansia* and higher levels of TM7 bacteria and Proteobacteria are linked with the increased levels of TNF-α in aged mice (Fransen et al. 2017). Thevaranjan et al. found that age-associated microbial dysbiosis can lead to increased gut permeability and circulating bacterial products, systemic inflammation, and macrophage dysfunction, but these changes can be reversed by anti-TNF-α therapy (Thevaranjan et al. 2017). In centenarians, the enrichment of Proteobacteria and a decrease in butyrate-producing bacteria are correlated with systemic increases in the pro-inflammatory cytokines IL-6 and IL-8 (Biagi et al. 2010). IL-6 strongly correlates with morbidity (frailty, sarcopenia, and a variety of age-related diseases), and mortality in older humans, and it has been verified as the most informative single marker of inflammaging and health status in elderly. The phylum Proteobacteria contains a group of bacteria redefined as pathobionts, which may escape surveillance, overtake mutualistic symbionts and induce pathology, while butyrate induces transforming growth factor-β secretion by epithelial cells, and triggers the production of IL-10 and retinoic acid by dendritic cells and macrophages (Shapiro et al. 2014). Clark et al. used the *Drosophila* fly model to study the relationships between microbiota dynamics, physiological decline of the aging intestine, and the ultimate manifestation of the aging process: death. They found that gut dysbiosis that follows age-onset gut barrier dysfunction induces systemic immune activation via the JAK-STAT pathway, which is a primary cause of mortality (Clark et al. 2015). Increasing gut microbiota lipopolysaccharide (LPS) levels can accelerate inflammaging by inducing p16 (a marker of senescence in vivo) and SAMHD1 expression (a novel marker of inflammaging) and nuclear factor (NF)-κB activation in mice (Kim et al. 2016). In addition, activation of tryptophan (Trp) metabolism along the kynurenine (Kyn) pathway prevents hyperinflammation and induces long-term immune tolerance (Sorgdrager et al. 2019). Reduced plasma levels of Trp are related to increased immune activation and can contribute to inflammaging (Rampelli et al. 2013). The gut microbiota of older people and centenarians is enriched in bacteria that consume Trp, affecting its bioavailability, and a corresponding reduction in Trp in the plasma of centenarians has been observed (Collino et al. 2013; Franceschi et al. 2017). Guedj et al. recently revealed that the gut microbiota can shape inflammaging cytokines, which results in age-dependent decline in DNA damage repair (Guedj et al. 2020). Decreased proteostasis and autophagy in aging can lead to the accumulation of extracellular waste products and activation of pattern recognition receptors (PRRs), which may lead to inflammasome assembly and consecutive secretion of proinflammatory mediators via different signaling pathways. However, inflammaging can be reversed by inhibiting these pathways, which can reduce the risk of age-related diseases and possibly enhance longevity. Jeong et al. found that *Lactobacillus brevis* OW38 treatment may ameliorate aging-associated colitis and memory impairment by inhibiting gut microbiota LPS production, NF-κB activation, and p16 expression (Jeong et al. 2016). Calorie restriction, which has a potent anti-inflammaging effect, has been demonstrated to induce dramatic changes in the gut microbiota. Pan et al. also observed that *Lactobacillus murinus* CR147 can be promoted by calorie restriction and helps attenuate aging-associated inflammation (Pan et al. 2018). As mentioned above, it suggests that gut microbiota modulations via dietary or probiotics is an useful anti-inflammaging intervention that can counteract the progression of age-related diseases.

Another factor associated with the aging process is immunosenescence, which may be defined as the decline in immunity with age. It represents a potential causative factor for many age related illnesses. Together with inflammaging, immunosenescence is suggested to stand at the origin of most of diseases of the elderly, such as infections, cancer, autoimmune disorders, and chronic inflammatory diseases. Immunosenescence and inflammaging do not have a unidirectional relationship; rather, they exist in a mutually maintained state where immunosenescence is induced by inflammaging and vice versa. Recent cumulative data suggest that human longevity would be dramatically shortened without the existence of the immunosenescence/inflammaging duo (representing two sides of the same phenomenon) (Fulop et al. 2018). Although the significance of immunosenescence in age-related alterations of the immune system is still controversial, it is conceivable that immunosenescence that leads to age-associated immunological dysfunction, may be a major contributor to the increased frequency of morbidity and mortality among the elderly (Fulop et al. 2018). Immunosenescence changes result in both quantitative and qualitative modifications of specific cellular subpopulations such as T cells, macrophages and natural killer (NK) cells as opposed to a global deterioration of the immune system. Neutrophils and macrophages from aged hosts are less active with diminished phagocytosing capability; for example, clearance of senescent cells by macrophages is reduced (Oishi and Manabe 2016; Amsterdam and Ostrov 2018). Macrophages are part of an integrated and highly evolutionary conserved set of functions crucial for survival, and these cells counteract all kinds of potentially harmful stressors impacting the body. Thevaranjan et al. observed that a higher proportion of germ-free mice live to 600 days compared to their conventional counterparts, and macrophages derived from aged germ-free mice maintain anti-microbial activity (Thevaranjan et al. 2017). Sharma et al. found that high accumulation of regulatory T cells (Tregs) prevents immune response activation in aged animals, while Tregs depletion may be critical for restoring immune responses (Sharma, Dominguez, and Lustgarten 2006). It is clear that the gut microbiota impacts systemic immunologic and inflammatory responses over the life of the human host. The profiles of the gut microbiota are also known to alter with aging and these changes have been linked to the declines in

immunity observed in immunosenescence. Recent studies suggested that maintenance of a "youthful" or "healthy" gut microbiota architecture during aging may delay or limit immunosenescence (Biagi et al. 2013). As mentioned above, age-related changes lead to elevated inflammatory cytokine levels among elderly subjects as compared to young adult. For example, age-related increases in TNF-α, IL-6, and IL-8 appear to be associated with alterations in the gut microbiota that influence host responses to commensal and pathogenic organisms (Biagi et al. 2010). Age-related alterations in antimicrobial peptides also represent important changes in an innate immune molecule that helps eliminate microbial pathogen in healthy young adults s. These peptides regulate mainly the $CD4^+$ cell compartment such as Th1, Th2, and Th17 responses to the gut microbiota. These observations demonstrate altered immune reactivity against gut microbes in aged individuals (Castaneda-Delgado et al. 2017). Regulating immunosenescence in elderly via modulating the gut microbiota is therefore a promising therapeutic strategy to combat aging. Oral supplementation with *Bifidobacterium*, can increase lymphocyte proportions, improve the anti-tumoricidal activity of NK cells, and restore phagocytosis in peripheral blood mononuclear cells and neutrophils; these effects are most evident in individuals 70 years of age and older, as well as those with the greatest degree of cellular immunosenescence (Thevaranjan et al. 2018). Fructooligosaccharides supplementation can reduce IL-6 mRNA expression and the phagocytic activity of granulocytes and monocytes in elderly subjects, while administration of β-galactooligosaccharides to elderly subjects increases mononuclear cell phagocytosis, NK cell activity, and IL-10production along with reductions of IL-6, IL-1β, and TNF-α (Clements and Carding 2018). Besides probiotics and prebiotics, Cho et al. observed that the polyphenolic lignan syringaresinol (SYR) significantly increases the Firmicutes/Bacteroidetes ratio compared with age-matched controls by increasing beneficial bacteria, *Lactobacillus* and *Bifidobacterium*, while reducing the opportunistic pathogenic genus *Akkermansia* (Cho et al. 2016). Accompanied with the alterations of gut microbiota, this delays immunosenescence by enhancing the numbers of total $CD3^+$ T cells and naïve T cells, inducing the expression of Bim, activating FOXO3 in $Foxp3^+$ Tregs and reducing serum level of LPS-binding protein (LBP, an inflammatory marker). These findings suggest that SYR may rejuvenate the immune system through modulation of gut integrity and microbiota diversity/composition in middle-aged mice, which may delay aging-associated immunosenescence. In addition, calorie restriction also modulates the gut microbiota structure to a more balanced state, thereby alleviating metabolic syndrome during aging and involving age-related immunosenescence regulation (Zhang et al. 2013; Pan et al. 2018). Therefore, reconstitution of a normal or healthy microbiota in the elderly has been proposed as an anti-immunosenescence intervention strategy.

The gut microbiota and human aging diseases

The dynamic transition of the gut microbiota from birth to old age influences host health and diseases across their lifespan. The enteral system provides functional connectivity with other organs and tissues of the body such as the brain, liver, heart, skin, muscle, pancreas and bone, referred to as gut-extraenteric tissue axis. Many aspects of this functional connectivity are mediated by the activities of the gut microbiota. Age-related changes of the gut microbiota appear to influence the onset and progression of enteric and extraenteric diseases, including sarcopenia and physical frailty, neurodegenerative diseases, nonalcoholic fatty liver disease (NAFLD), *Clostridium difficile* infection (CDI), colorectal cancer, coronary heart disease, metabolic syndrome, and others (Singh et al. 2019). Prior to occurrence of these aging-related diseases, bidirectional interactions between the gut and extraenteric tissue will change first. Given the importance of the gut microbiota in the human body, it has been suggested that gut-extraenteric tissue axis aging may be more suitable to decipher healthy and non-healthy aging in humans. Clarifying the possible pathophysiological roles of the aged gut microbiota in these diseases may lead to the development of novel anti-aging interventions (Figure 2).

Gut itself aging diseases

Gut aging is associated with a reduction in the beneficial commensal microbes, which controls the expansion of pathogens and maintains the integrity of the intestinal barrier through the production of mucus and lipid metabolites (e.g., SCFAs), which cause inflammatory conditions in elderly individuals. Alterations of the gut microbiota in aged individuals are associated with increased incidences of enteric diseases such as colon cancer, pathogens such as CDI, and other bowel disorders. Colon cancer is a common cancer, and its prevalence is expected to rise as aging population grows (Wong et al. 2020). In line with the aged-type gut microbiota alterations, we previously found that Lactobacillales was enriched in cancerous tissue, whereas *Faecalibacterium* was reduced. In the mucosa-adherent microbiota, *Fusobacterium*, *Porphyromonas*, *Peptostreptococcus*, and *Mogibacterium* were enriched in cancer patients, whereas SCFA-producing bacteria such as *Bifidobacterium*, *Faecalibacterium*, and *Blautia* were reduced (Chen et al. 2012). Yu and her colleagues demonstrated that *Fusobacterium nucleatum*, *Parvimonas micra*, *Peptostreptococcus anaerobius*, *Solobacterium moorei*, and enterotoxigenic *Bacteroides fragilis* can serve as novel noninvasive diagnostic biomarkers for colorectal cancer (Liang et al. 2017; Yu et al. 2017; Long et al. 2019), while the amount of *Fusobacterium nucleatum* DNA in colon cancer tissue is associated with shorter survival and may serve as a prognostic biomarker (Mima et al. 2016). The mechanisms underlying the interaction between gut dysbiosis and colorectal carcinogenesis in the elderly include the promotion of inflammation, pathological bacteria adhesion and induction of tumorigenesis (Yang and Yu 2018). Growing evidence indicates that the aged-type gut microbiota is closely associated with colon cancer initiation and development. In theory, it would be possible to lower the risk of cancer through modulating the gut microbiome by dietary control or

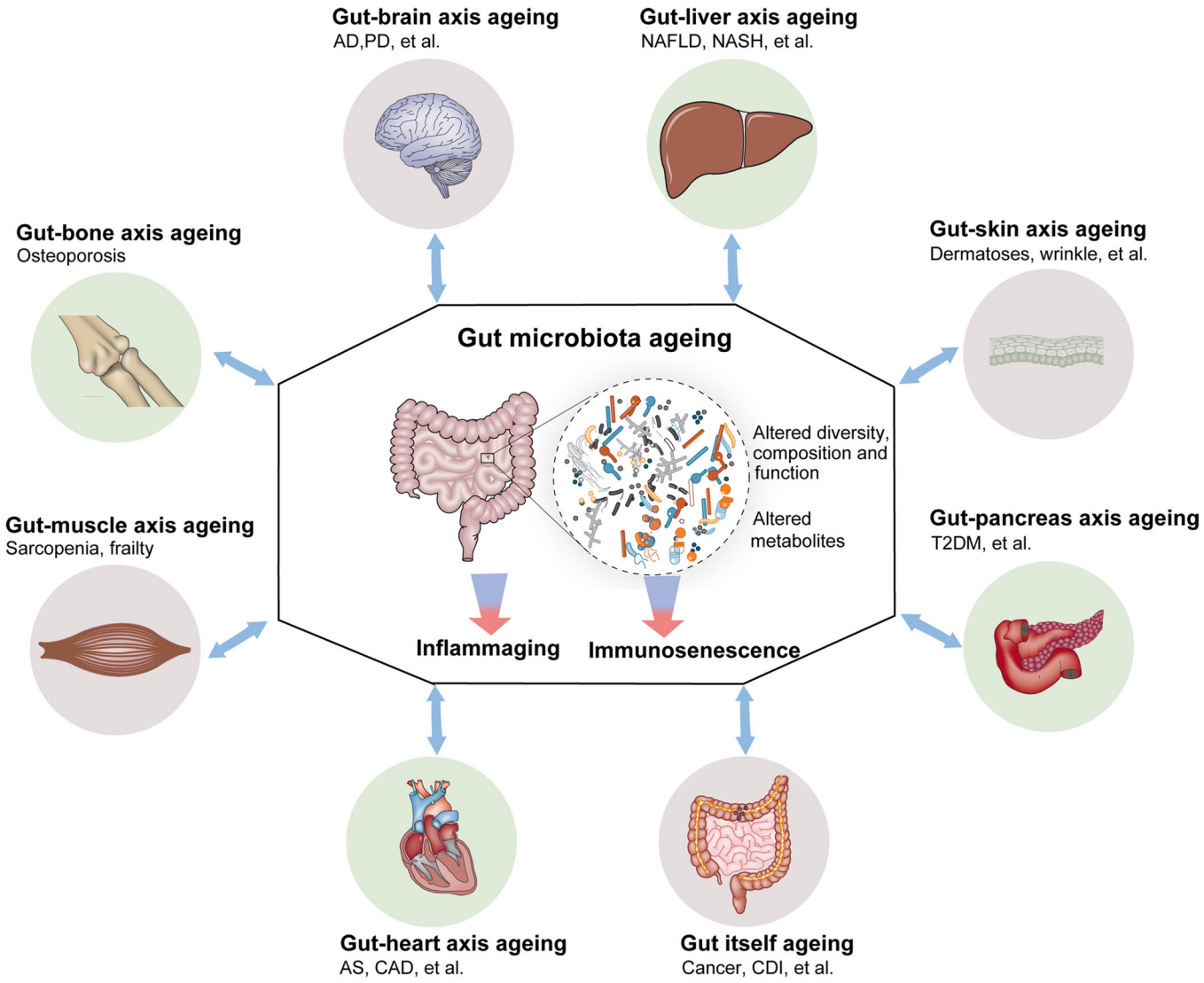

Figure 2. Gut microbiota and human aging diseases.

antibiotic treatment to eliminate tumor associated bacterial pathogens.

CDI is a common cause of health care-associated diarrhea, and is associated with significant morbidity, mortality, and health care costs. Age-related impairment of the immune system, increasing antibiotic utilization, and frequent health care exposure may be the main risk factors for CDI in the elderly, but the highest risk factor is systemic antimicrobial therapy (Asempa and Nicolau 2017). Antibiotic exposure can trigger a structural and functional imbalances of the gut microbiota and destroy the colonization resistance of the healthy microbiota, allowing the opportunistic pathogen grow rapidly. A high bacterial load of *Clostridium difficile* is an independent predictor of poor clinical outcome (Reigadas et al. 2017). Our group observed that putative butyrate-producing anaerobic bacteria were significantly depleted whereas endotoxin-producing opportunistic pathogens and lactate-producing phylotypes increased dramatically in CDI patients (Gu et al. 2016). In a mouse model of CDI, Shin et al. revealed that aged mice have significant deficiencies in the Bacteroidetes phylum (specifically *Bacteroides* and *Alistipes*) while microbiota exchange by cage switching improved survival and early immune response in aged CDI mice (Shin et al. 2018). van Opstal et al. also showed that disease severity, likelihood of relapse, and mortality were increased, and recovery from infection was delayed, in aged mice compared to young mice (Van Opstal et al. 2016). These findings have tied aged gut microbiota structure and function to local and systemic immune responses and to host outcome after pathogen encounters, which suggests that gut microbiota manipulation, not only single microbe but the overall microbial community, may be a useful strategy to combat age-related pathogen colonization.

Gut-muscle axis aging

The gut-muscle axis refers to the roles for the gut microbiota on the maintenance of whole body lean mass, skeletal muscle mass, and physical function (De Sire et al. 2018; Grosicki, Fielding, and Lustgarten 2018; Ni Lochlainn, Bowyer, and Steves 2018; Picca et al. 2018; Ticinesi et al. 2019). Gut-muscle axis aging, mainly sarcopenia and

physical frailty, is characterized by loss of muscle mass and lower muscle function, which increase the risk of negative outcomes such as falls, fractures, disability and mortality. The mechanisms of gut-muscle axis aging include inflammaging, immunosenescence, anabolic resistance and increased oxidative stress (Soysal et al. 2017; Wilson et al. 2017). Evidence from human studies shows that gut microbiota alterations correlated with increased frailty (Van Tongeren et al. 2005; Claesson et al. 2012). Studying 728 women from the TwinsUK cohort (age range, 42–86 years), Jackson et al. observed that frailty was negatively associated with alpha diversity of the gut microbiota (Jackson et al. 2016). The decreased relative abundance of *Faecalibacterium* and *Bifidobacterium* in aged gut microbiota are negatively correlated with muscle strength, while *Eubacterium dolichum* and *Eggerthella lenta* positively associated with frailty (Van Tongeren et al. 2005; Biagi et al. 2010). Nay et al. found that in antibiotic-treated mice, running endurance is decreased and the extensor digitorum longus muscle fatigue index was lower in an ex vivo contractile test, while muscle mass and the muscle mass/body weight ratio increased following natural microbiota seeding to restore the gut microbiota (Nay et al. 2019). These results suggested that a healthy gut microbiota is required for host optimal skeletal muscle function. In addition, oral supplements of specific probiotic strains such as *Lactobacillus casei* or *Bifidobacterium longum* can increase the muscle mass/body weight ratio without affecting body weight in aged mice by the regulation of the gut microbiota (Ni et al. 2019). Claesson et al. suggested that the gut microbiota can influence skeletal muscle homeostasis and physical function via microbiota-dependent metabolites such as SCFAs (Claesson et al. 2012). Reduced gut levels of SCFAs represent a pro-inflammatory gut microenvironment. The observed negative associations of frailty with butyrate producers support the role of butyrate in suppressing frailty-associated inflammation. Saint-Georges-Chaumet and Edeas also found that microbiota-derived SCFAs exert profound influences on skeletal muscle cell function by promoting mitochondrial activity (Saint-Georges-Chaumet and Edeas 2016). Both animal and human studies indicated that the gut microbiota might be actively involved in the pathogeneses of sarcopenia and physical frailty, and could represent a reasonable therapeutic target.

Gut-brain axis aging

The gut-brain axis refers to the functional relationship between the gut and brain, which is controlled by the gut microbiota, gut hormones, enteric nervous system, central nervous system, and nutrients. These components bidirectionally interact through neurohumoral pathways and direct connections between the vagus nerve and brainstem, and between the spinal nerves and spinal cord (Cryan et al. 2019). It is now being recognized that the gut microbiota is a key modulator of brain and behavior. In the elderly, conditions including Alzheimer's disease (AD) and Parkinson's disease (PD) are associated with gut microbiota changes. AD is an age-related neurodegenerative disease characterized by slowly progressive memory decline and cognitive dysfunction that has long been associated with bacterial infections and inflammation-causing immunosenescence (Alzheimer's Association 2019). The structure and composition of the gut microbiota are significantly altered in elderly subjects with AD, which can increase intestinal permeability and induce inflammation that have been shown to increase the risk of AD (Wang, Sun, et al. 2019). Vogt et al. identified phylum-through genus-wide differences in bacterial abundance including decreased Firmicutes, increased Bacteroidetes, and decreased Bifidobacterium in the gut microbiota of AD participants (Vogt et al. 2017). Zhuang et al. observed that the relative abundance of Ruminococcaceae, Enterococcaceae, and Lactobacillaceae increased, while those of Lanchnospiraceae, Bacteroidaceae, and Veillonellaceae decreased significantly in AD patients compared with the control group (Zhuang et al. 2018). The decreased in Bacteroides in AD patients, especially *Bacteroides fragilis*, was significantly correlated with cognitive impairment and brain amyloidosis (Cattaneo et al. 2017). An animal study also found that *Bifidobacterium* has a positive impact on cognition in an anxious mouse strain after daily feeding for 11 weeks (Savignac et al. 2015). These bacteria can produce metabolites such as neurotransmitters (e.g., γ-aminobutyric acid, serotonin), neuropeptides, endocrine hormones, and immunomodulators, which are all related to AD (Alkasir et al. 2017). Mahmoudian Dehkordi et al. found that an altered gut microbiota dysbiosis-associated bile acid profile was associated with cognitive impairment in patients with AD in a large multicenter study (Mahmoudiandehkordi et al. 2019). Wang et al. observed that gut dysbiosis leads to peripheral accumulation of phenylalanine and isoleucine that stimulates the differentiation and proliferation of pro-inflammatory T helper 1 (Th1) cells. Brain-infiltrated peripheral Th1 immune cells are associated with M1 microglia activation, contributing to AD-associated neuroinflammation (Wang, Sun, et al. 2019). Recently, Haran et al. observed that the AD gut microbiota shows a lower proportion and prevalence of bacteria with the potential to synthesize butyrate, as well as higher abundances of taxa that are known to cause proinflammatory states (Haran et al. 2019). AD gut dysbiosis can affect intestinal health via dysregulation of the P-glycoprotein pathway, while directly contributing to inflammatory disorders of the intestine. They identified a novel potential nexus between the gut microbiota, loss of intestinal homeostasis, and inflammation that may underlie AD. Sun et al. reported that gut microbiota modulation via fecal microbiota transplantation (FMT) can improve cognitive deficits and reduce brain deposition of amyloid-β (Aβ) by decreasing phosphorylation of tau protein and the levels of Aβ40 and Aβ42 and increasing synaptic plasticity (Sun, Xu, et al. 2019). However, most of these studies focused on the association between the gut microbiota and AD, the precise cause-effect relationships will need to be determined to clarify the roles and mechanisms of gut bacteria in the progression or maintenance of AD. From correlation to causation, targeting the gut microbiota or its metabolites may

lead to novel interventional approaches that are protective against AD.

PD represents another growing health concern for an ever-aging population. This progressive disease affects the central nervous system and eventually the motor system. Many high-throughput sequencing studies have confirmed that gut microbiota dysbiosis occurs in patients with PD (Unger et al. 2016; Hill-Burns et al. 2017; Petrov et al. 2017; Lin et al. 2018; Qian et al. 2018). A 2-year follow-up study found that specific bacterial taxa such as *Roseburia*, *Prevotella* and *Bifidobacterium* differed between patients and controls at both baseline and 2 years later, and progressed PD patients had a Firmicutes-dominated enterotype more often than stable patients or control subjects. Additionally, *Prevotella*, a genus already shown to be reduced in PD patients compared to controls, was also less abundant in patients with faster disease progression (Aho et al. 2019). Sampson et al. found that the gut microbiota can promote α-synuclein (αSyn)-mediated motor deficits and brain pathology, while gut bacteria depletion reduces microglia activation, and bacteria metabolites such as SCFAs can modulate microglia and enhance PD pathophysiology (Sampson et al. 2016). SCFAs can regulate microglia homeostasis and promote their full maturation and inflammatory capabilities (Erny et al. 2015). Insoluble aggregates and oligomeric forms of αSyn can also activate microglia. Intriguingly, αSyn aggregation can be enhanced by an inflammatory environment, which may further activate microglia upon contact and promote a feed-forward cascade that leads to additional αSyn aggregation and propagation and progression of PD (Gao et al. 2011). Dopamine modulators are a first-line therapeutic in PD; however, the efficacy of levodopa (L-dopa) treatment for PD is highly variable between individuals (Jenner 2008). Maini Rekdal et al. recently found that the efficacy of L-dopa treatment for PD is dependent on the composition of their microbiota. L-dopa is decarboxylated into active dopamine, but if the gut microbiota metabolize L-dopa before it crosses the blood-brain barrier, the medication is ineffective. Tyrosine decarboxylase from *Enterococcus faecalis* and dopamine dehydroxylase from *Eggerthella lenta* A2 sequentially metabolize L-dopa into m-tyramine (Maini Rekdal et al. 2019; Van Kessel et al. 2019). In addition, the higher relative abundance of bacterial tyrosine decarboxylases at the site of L-dopa absorption in the proximal small intestine had a significant impact on plasma levels of L-dopa in rats. The increased relative abundance of *Enterococcus faecalis* can explain the increased dosage regimen of L-dopa in PD patients (Van Kessel et al. 2019). Understanding the interaction between the gut microbiota and PD occurrence may open new avenues for PD intervention and therapy.

Gut-liver axis aging

The gut-liver axis refers to the functional and structural connectivity between the gut and the liver that ensures regulated bidirectional movement of substances between the two organs to maintain homeostasis. During aging, hepatic changes such as increased hepatocyte size, more binucleated cells, and a reduction in mitochondrial number have been reported, which can affect liver morphology, physiology, and oxidative capacity. Evidence indicates that aging predisposes to hepatic dysfunction and inflammation that can contribute to the development of geriatric NAFLD/nonalcoholic steatohepatitis (NASH). NAFLD is described as a multifactorial complication due to the genetic predisposition, metabolic functions, inflammatory, gut microbiota, and environmental factors. Among these gut microbiota dysbiosis and related gut mucosal barrier dysfunction are closely correlated to NAFLD development, which implies gut-liver axis impairment. Experiments using gut microbiota transplants to germ-free animal models showed that NAFLD development is influenced by gut bacteria (Celaj et al. 2014). Using 16S rRNA gene sequencing, Boursier et al. characterized the association between NAFLD severity and gut dysbiosis in patients over 60 with biopsy-proven NAFLD. They found that NAFLD severity was associated with a shift in the metabolic function of the gut microbiota such as carbohydrate, lipid, and amino acid metabolism in elderly patients (Boursier et al. 2016). The relative abundances of *Bacteroides* and *Ruminococcus* were significantly increased in patients with NAFLD. *Bacteroides* is negatively correlated with fecal SCFAs and amino acids, and decreased SCFAs might be detrimental for NAFLD (Puertollano, Kolida, and Yaqoob 2014). In addition, *Bacteroides* accumulation correlated with an accumulation of branched-chain fatty acids that are produced by amino acid fermentation. The latter is known to promote insulin resistance, which increases the risk for NAFLD (Newgard 2012). Intriguingly, the increases in fecal *Bacteroides* abundance were paralleled by decreases in *Prevotella*, which suggests that *Bacteroides* and *Prevotella* are competitors in the gut microbiota and that the balance between them is involved in NAFLD development (Boursier et al. 2016). Zhu et al. also found that NASH patients had an increased abundance of alcohol-producing bacteria that could increase serum alcohol levels and oxidative stress, resulting in liver injury (Zhu et al. 2013). In fact, NAFLD can be affected in different ways by the gut microbiota including increased gut permeability and facilitation of the passage of LPS and other inflammatory factors to the blood, decreased choline availability, changes in bile acid composition and increased ethanol production in the intestine (Safari and Gerard 2019). Given the lack of effective pharmacologic interventions for aged NAFLD, restoring the gut microbiota to reverse dysbiosis seems like a potential therapeutic strategy. In term of these aforementioned mechanisms, there are many ways to treat NAFLD that target gut microbiota modulation via antibiotics, prebiotics, probiotics, or a combination of both prebiotics and probiotics (synbiotics) (Olveira and Gonzalez-Molero 2016; Safari and Gerard 2019). The most frequently mentioned probiotics in recent clinical trials are *Lactobacilli*, *Streptococci*, and *Bifidobacteria*. Xie et al. summarized 26 randomized controlled trials that compared probiotics and/or synbiotics versus placebo in NAFLD patients from January 2010 to June 2019; they found that probiotics/synbiotics can improve transaminase levels, hepatic steatosis, and NAFLD activity score, and

reduce proinflammatory cytokines such as TNF-α and the IL family (IL-1, IL-6, IL-8) (Xie and Halegoua-Demarzio 2019). The prebiotic spirulina can modulate the gut microbiota (increases in *Roseburia* and *Lactobacillus* proportions) and activate the immune system in the gut, which can ameliorate the hepatic inflammation in aged mice (Neyrinck et al. 2017). The properties of safety, efficacy, and good tolerance suggest that probiotics/prebiotics/synbiotics may be a promising therapeutic strategy for individuals with NAFLD, especially the elderly.

Gut-heart axis aging

The gut-heart axis refers to the functional relationship between the gut and the heart. Accumulating evidence suggests that the gut microbiota plays a key role in regulating gut-heart axis crosstalk during atherosclerosis (AS) progression. Both epidemiological and animal studies have shown that the gut microbiota can regulate cardiometabolism and microcirculatory disturbances, which are associated with atherosclerotic cardiovascular disease (Turnbaugh et al. 2006; Wang et al. 2011; Mulders et al. 2018; Toya et al. 2020). Various hormones including glucagon-like peptide 1 (GLP-1), glucagon, and insulin can link the gut and heart, and these can be affected by gut microbiota composition and bacterial metabolites such as SCFAs (Petersen et al. 2014; Lach et al. 2018; Soto et al. 2018). In the elderly, the abundance of genus *Bacteroides* is lower in patients with coronary artery disease (CAD) than in patients without CAD with coronary risk factors or in healthy volunteers (Emoto et al. 2016; Emoto et al. 2017). At the species level, 16S ribosomal RNA gene sequencing revealed significantly lower abundances of *Bacteroides vulgates* and *Bacteroides dorei* in patients with CAD. Translational research demonstrated that gavage with live *Bacteroides vulgates* and *Bacteroides dorei* attenuate atherosclerotic lesion formation in AS-prone mice, markedly ameliorating endotoxemia followed by decreasing gut microbial LPS production, effectively suppressing proinflammatory immune responses (Yoshida et al. 2018). Another study identified *Chryseomonas*, *Veillonella*, and *Streptococcus* in AS plaque samples, and several bacterial phylotypes from the gut are common to atherosclerotic plaques, which are correlated with cholesterol levels (Koren et al. 2011). Tuomisto et al. found that *Clostridium leptum*, Enterobactericeae and *Streptococcus* increase in the gut microbiome in an age-dependent manner and can be detected in the same individual's coronary plaques, associating with more severe coronary AS (Tuomisto et al. 2019). Similarly, a metagenome-wide association study of stools found that *Enterobacteriaceae* and *Streptococcus* are enriched in CAD patients compared with healthy controls (Jie et al. 2017). Through multi-omics analyses, Liu et al. found that several bacterial co-abundance groups (CAGs) and metabotypes exhibit significant changes with CAD development and may be used independently as biomarkers for CAD subtype diagnosis. They also showed that four CAGs containing operational taxonomical units from Lachnospiraceae and Ruminococcaceae (major members of the human gut that produce butyrate) are significantly reduced with CAD development (Liu, Chen, et al. 2019). The largest comprehensive metagenome-based association study in elderly recently performed by Kurilshikov et al. also identified numerous associations of functional properties and microbial species in the gut microbiome with plasma metabolic traits, including lipoprotein particle composition, fatty acid saturation, and glycoprotein N-acetyls, which are closely related to the CAD development (Kurilshikov et al. 2019). In fact, bacteria with the capacity to produce butyrate, trimethylamine-N-oxide (TMAO), endotoxin (LPS), and phenylacetyl glutamine (PAGln) have been found to play roles in the gut-heart axis in AS. The reduction of butyrate and increases of microbial-derived TMAO, LPS, and PAGln impair gut-heart axis balance and promote AS development. Harmful substances such as TMAO and PAGln have been considered as potential biomarkers of coronary heart disease (Chen, Zhang, Wu, et al. 2020). Butyrate can inhibit intestinal permeability, so fewer molecules of LPS, TMAO, and PAGln can reach the general circulation and induce systemic inflammation, which could regulate macrophages and contribute to atherosclerotic plaque formation (Fluitman et al. 2018; Bastin and Andreelli 2020). In line with its functions, butyrate-producing bacteria such as *Roseburia intestinalis*, *Butyrivibrio crossotus* and *Faecalibacterium prausnitzii* are also depleted in atherosclerotic cardiovascular disease, suggesting that butyrate plays a key role in reducing AS development and maintaining the gut-heart axis balance via butyrate-producing bacteria (Chen, Zhang, Wu, et al. 2020). As a necessary amino acid, taurine can regulate gut microbiota by inhibiting the growth of harmful bacteria, accelerating SCFA production, and reducing LPS concentrations (Yu et al. 2016). These findings may contribute to the development of preventive or therapeutic strategies aimed at modulating the gut microbiota to reduce cardiovascular event burden in adults and the elderly.

Gut-pancreas axis aging

The gut-pancreas axis refers to structural and functional cross talk between the gut and pancreas that ensures regulated functioning of both organs. In the gut, food substances can trigger the release of certain molecules to influence endocrine pancreatic functions, whereas substances released from the endocrine pancreas modulate exocrine pancreatic secretory activity as well as metabolic functions. Aging is one of the risk factors for type 2 diabetes mellitus (T2DM). Incidence data for T2DM in the elderly are sparse, but they indicate that the prevalence of diabetes greatly increase with age. T2DM is a major risk factor for metabolic syndrome, cardiovascular disease, and cerebral vascular diseases in the elderly (Ferri et al. 2005). Increasing evidence indicates that gut microbiota is associated with T2DM (Qin et al. 2012; Karlsson et al. 2013; Wu et al. 2017). In a metagenome-wide association study of 345 Chinese subjects, Qin et al. found that T2DM patients exhibit a moderate degree of gut microbial dysbiosis, a decrease in the abundance of some universal butyrate-producing bacteria, an increase in various

opportunistic pathogens, and an enrichment of other microbial functions conferring sulfate reduction and oxidative stress resistance (Qin et al. 2012). However, this study did not consider the influence of confounders such as age on the gut microbiota. One recent study enrolling Nigerian elderly with and without T2DM found that the overall structure of the gut microbiota from elderly subjects with T2DM are significantly different compared to healthy volunteers. *Ruminococcus*, *Collinsella*, and Bifidobacteriaceae are enriched in elderly individuals with T2DM, while members of Clostridiaceae and Peptostreptococcaceae are enriched in healthy volunteers (Afolayan et al. 2020). One study performed FTM from T2DM mice into germ-free mice and verified that T2DM-associated gut dysbiosis contributes to the development of T2DM and that potential therapeutic strategies improving gut microbiota may provide beneficial effects for individuals with T2DM and age-related glucose intolerance (Yu et al. 2019). Microbial metabolites also play an important role in T2DM development. Liquid chromatography-mass spectrometry fecal metabolomics profiles showed that several metabolites such as L-tyrosine, LysoPC, protorifamycin I, pimelic acid, epothilone A, 7-dehydro-desmosterol, L-lysine, and teasterone are enriched in T2DM patients; these are involved in metabolic processes including carbohydrate metabolism, starch and sucrose metabolism, phenylpropanoid biosynthesis, and biosynthesis of amino acids (Nuli et al. 2019). These metabolic alterations are associated with low-grade inflammation that contributes to the onset of T2DM. Chinese researchers have found that dietary inulin can alleviate the diverse stages of T2DM by suppressing fasting blood glucose, body weight, glycated hemoglobin, blood lipid, plasma LPS, IL-6, TNF-α, and IL-17A and modulating the gut microbiota (Li et al. 2019). In addition, the gut microbiota can mediate intermittent-fasting alleviation of T2DM and related cognitive impairment (Liu et al. 2020). These compelling lines of evidence support the concept that the gut microbiota participates in the development of insulin resistance and low-grade inflammation associated with T2DM, and gut microbiota modification may be a potential therapeutic strategy to treat T2DM in elderly.

Gut-bone axis aging

The gut-bone axis represents functional crosstalk between epithelial cells of the gut and the bone cells (osteoblasts and osteoclasts). The gut microbiota is a key regulator of bone health that affects skeletal development and involution (Zaiss et al. 2019). Age associated alterations in gut microbiota composition and host responses to the microbiota contribute to skeletal abnormalities, characterized by reduced bone mineral density, increased fracture risk, and/or joint inflammation. This pathological process is characterized by altered immune cell activity and elevated inflammatory cytokines in the bone marrow microenvironment due to a disrupted gut immune response. The gut and bone marrow are two representative central reservoirs of immune cells. Gut microbiota alterations can promote an inflamed gut environment, driven by unrestrained immune cell activation and increased pro-inflammatory cytokine production, resulting in increased inflammation in bone marrow microenvironments and subsequently decreased bone mass (Ke, Arra, and Abu-Amer 2019). Linkers in the gut-bone axis, such as insulin-like growth factor 1 (IGF-1) (Yan et al. 2016; Novince et al. 2017) and hydrogen sulfide (H_2S) (Linden 2014) can be regulated by the gut microbiota and microbial products. SCFAs recently received attention for their capacity to regulate bone resorption and formation; they have been identified as potent regulators of osteoclast metabolism and bone homeostasis. SCFAs can affect bone homeostasis via two routes: by directly blunting osteoclast differentiation and inhibiting histone deacetylase activity, and by indirectly inducing Tregs to suppress osteoclast differentiation via anti-osteoclastic cytokine secretion. Among the SCFAs, butyrate and propionate exert anti-osteoclastic effects on osteoclast differentiation in experiments using mice and human primary cultured cells (Cantley et al. 2011; Pham et al. 2011). An animal study reported that supplemental treatment with SCFAs can restore serum IGF-1 and bone mass levels in antibiotic-treated mice, suggesting that SCFAs can regulate the host skeleton (Yan et al. 2016). However, butyrate and propionate levels are significantly decreased in elderly, which might explain the aging-related bone loss. Multiple studies found that supplementation of specific microbial members such as *Lactobacillus reuteri*, *Lactobacillus rhamnosus* GG (LGG), *Lactobacillus paracasei* and/or *Lactobacillus plantarum* in OVX mice limited bone loss by dampening osteoclastogenic cytokine production in bone marrow and/or intestine due to estrogen deficiency (Britton et al. 2014; Ohlsson et al. 2014; Li et al. 2016). Tyagi et al. found that LGG treatment can increase the levels of Clostridia, which can induce the production of intestinal and circulating butyrate (Tyagi et al. 2018). This finding confirms that butyrate is capable of stimulating bone formation and increasing trabecular bone volume without affecting cortical bone. Based on experimental data, the gut microbiota regulates bone metabolism via regulating host metabolism, the immune response, and endocrine factors. Restoration of the gut microbiota directly or indirectly with prebiotics, probiotics, synbiotics, or postbiotics may help treat aging-related bone diseases.

Gut-skin axis aging

The gut-skin axis is a functional relationship between the gut and skin that ensures adequate regulation of cutaneous functions. Skin homeostasis is linked with the gut; thus, accounting the bidirectional communication between both organs (Ahlawat, Asha, and Sharma 2020). During aging, visible and functional changes occur at all levels of the skin structure, modifying its appearance. Skin resident cells become senescent, and the extracellular matrix (mainly in the dermis) is progressively damaged, which affects normal skin organization and its capacity for repair (Bonte et al. 2019). During the aging process, gut microbiota alterations have the potential to negatively impact skin function. Many gut dysbiosis associated gastrointestinal diseases such as

inflammatory bowel disease and celiac disease can affect skin health (Bonciani et al. 2012; Wu et al. 2013), and defined dermatoses show a strong association with these gastrointestinal diseases. A randomized double-blind placebo-controlled clinical study demonstrated that oral supplementation with *Lactobacillus paracasei* NCC 2461 (ST11) decreased skin sensitivity and increased barrier function in the treated group (Gueniche et al. 2014), underscoring the importance of a normal gut microbiota in skin health. Diminished integrity of the gut barrier with advanced age is believed to contribute to aging-associated dysfunction and pathologies that associated with the penetration of immunogenic molecules. These antigens can access the circulation, preferentially accumulate in the skin, and disrupt skin homeostasis, leading to chronic skin inflammation and a continuous immune response (O'neill et al. 2016). Gut *Clostridium difficile* produce metabolites such as free phenol and para-cresol, the biomarkers of an imbalanced gut microbiota, that can access the blood stream and accumulate in the skin, leading to reduced expression of keratin 10 in keratinocytes (Miyazaki et al. 2014). In contrast, daily intake of the probiotic *Bifidobacterium breve* together with galactooligosaccharide reduce serum total phenol levels produced by the gut microbiota and improve skin health in healthy adult women (Miyazaki et al. 2014). In addition, SCFAs are gut microbiota-derived products that promote epithelial barrier integrity of the gut and exert anti-inflammatory effects. A clear reduction of SCFAs was observed in fecal samples from patients with atopic dermatitis (Reddel et al. 2019). The use of probiotics may restore a healthy gut microbiota, and the ratio of SCFA-secreting bacteria are increased in the gut in atopic dermatitis patients after treatment. In fact, SCFA concentrations decrease significantly along with the changed gut microbiota in aging populations. Secondary bile acids such as lithocholic acid and deoxycholic acid may impact skin physiology (Szanto et al. 2019). The production of secondary bile acids are mediated by *Bacteroides*, *Clostridium*, *Eubacterium*, *Lactobacillus*, and *Escherichia*, which are obviously decreased in aged subjects (Chen, Takeda, et al. 2019). Their changing patterns suggest that replenishing bacteria capable of synthesizing secondary bile acids may contribute to the maintenance of skin homeostasis. Besides, the gut microbiota can also modulate the functions of the skin by regulating immune responses. Though not yet fully explored, the mechanisms by which the gut microbiota exerts an influence on skin homeostasis appear to be related to the modulatory effect of the gut microbiota on systemic immunity. Schwarz et al. found that SCFAs—particularly butyrate—control skin immune responses via increasing Tregs (Schwarz, Bruhs, and Schwarz 2017). SCFAs have a significant role in controlling the prevalence of skin microbiota species that consequently affects the cutaneous immune response (Salem et al. 2018). The skin microbiota is an inseparable component of the skin barrier structure that participates in the stabilization or impairment of the barrier function, as well as the development of many skin diseases. A recent study found that the skin microbiota is closely related with age, with increasing bacterial richness and diversity and loss of skin-site selectivity in the elderly (Zhai et al. 2018). Increasing evidence indicates that the gut microbiota appears to influence the skin microbiota by producing SCFAs, which determines the predominance of certain skin microbiomic profiles. Several animal and human studies have documented the beneficial effects of gut bacteria on skin health and appearance. In animal studies, oral supplements of *Lactobacillus reuteri* can increase dermal thickness, enhance folliculogenesis, and increase sebocyte production which manifested as thicker, shinier fur (Levkovich et al. 2013). Ogawa et al. reported that *Lactobacillus brevis* SBC8803 treatment leads to decreased cutaneous arterial sympathetic nerve tone and increased cutaneous blood flow (Ogawa et al. 2016). A human clinical study demonstrated that SBC8803 can decrease transepidermal water loss and significantly increase corneal hydration (Ogawa et al. 2016), and *Lactobacillus paracasei* NCC2461 can decrease skin sensitivity and transepidermal water loss (Gueniche et al. 2014). Recently, Nam et al. found that *Lactobacillus plantarum* HY7714 (HY7714) consumption influences skin health through its modulatory effects on the gut microbiota and subsequent immune responses. RNA-sequencing analysis revealed its efficacy at restoring the gut barrier integrity by regulating gene expression associated with the extracellular matrix and immunity (Nam et al. 2020). These findings indicate that the gut microbiota intimately links the gut and skin, while crosstalk between the two offers targetable pathways with obvious therapeutic potential in dermatological practice.

Gut microbiota modulations in the elderly

The increased prevalence of aging-related diseases suggests that maintenance of gut microbiota eubiosis plays vital roles in healthy aging and longevity, which can be modulated via dietary intervention, microecological regulators, and FTM.

Dietary intervention

Diet is one of the most important extrinsic factors that shapes the makeup and activity of the resident gut microbiota. Different from healthy young adults, deterioration in dentition, salivary function, digestion, and intestinal transit time may change the dietary habitats and patterns such as the amount, type and balance of the main dietary macronutrients (carbohydrates, proteins and fats) in the elderly, which may underlie the microbiota-related acceleration of age-related health decline. Evidence indicates that regular consumption of a diet rich in fruits and vegetables is associated with a lower risk of age-related diseases. Reduced dietary intake of plant-based polysaccharides is often seen in the elderly, which can lead to the gut microbiota switching to other substrates, notably protein or amino acids. Generally, microbial metabolism of dietary carbohydrates results mainly in the formation of SCFAs and gases, which can lower colonic pH and inhibit pathogen overgrowth. However, the fermentation of amino acids, in addition to releasing beneficial SCFAs, produces a range of potentially

harmful compounds, of which ammonia, phenols, p-cresol, certain amines, and H_2S can contribute to intestinal diseases such as cancer or inflammatory bowel disease in animal models (Windey, De Preter, and Verbeke 2012). The Mediterranean diet (MedDiet) including polyunsaturated fatty acids, polyphenols, and antioxidants is one of the most recognized diets for disease prevention and healthy aging, partially due to its demonstrated anti-inflammatory and antioxidative properties. Evidence supports the widely recognized assumption that the MedDiet is independently associated with a higher level of successful aging (Foscolou et al. 2020), which is greatly beneficial for preventing aging-related diseases ranging from AS to cancer (Di Serio et al. 2016; Dhouafli et al. 2018; Chaari 2020). A previous study described a positive association between MedDiet and sarcopenia (Granic, Sayer, and Robinson 2019), while components of the MedDiet are considered to be neuroprotective (Shannon et al. 2019; Baranowski et al. 2020; Mantzorou et al. 2020) and cardioprotective (Corina et al. 2019), and can help improve glucose tolerance (Jennings, Cunnane, and Minihane 2020), prevent obesity (Barrea et al. 2020) and intestinal inflammation (Cariello et al. 2020; Serreli and Deiana 2020), and reduce frailty (Ghosh et al. 2020).

In addition, caloric restriction (CR) is one of the most effective interventions to prolong lifespan and promote health, but its effects are age dependent (Chen, Liao, et al. 2019). It can act as an intervention for weight control, but more importantly, as a strategy for healthy aging. A cohort of centenarians from Japan consumes 15 to 20% less energy than the average Japanese, which suggests that CR may be a physiological driver of longevity (Willcox et al. 2007). During the last decades, intermittent fasting (IF) has emerged as an unconventional approach to reduce body weight and improve metabolic health beyond simple CR. IF and CR can directly induce a gut microbiota composition shift that promotes browning of white adipose tissue and enhances brown adipose tissue activity. Li et al. observed that IF increases small intestinal length and causes clear alterations in gut microbiota content and composition in germ-free mice, resulting in a significantly increased ratio of Firmicutes/Bacteroidetes (Li et al. 2017) that reverses the aging-related changing patterns of the gut microbiota. Zhang et al. demonstrated that life-long CR mice have a *Lactobacillus*-predominated gut microbiota (Zhang et al. 2013). The altered aging gut microbiota plays a critical role in the pathogenesis of systemic inflammation. Attenuation of inflammation is one of the most important ways that CR can improve health during aging. Compelling evidence suggests that CR has a potent anti-inflammaging effect via modulating the gut microbiota (Pan et al. 2018). Mechanistically, this effect is linked to lower expression of the key bacterial enzymes necessary for the lipid A biosynthesis, a critical LPS building component. Decreased LPS dictates the tone of the innate immune response during CR, leading to increased eosinophil infiltration and anti-inflammatory macrophage polarization in the fat of CR animals (Fabbiano et al. 2018). One strain isolated from the feces of CR mice, *Lactobacillus murinus*, contributes to the protection of the gut barrier and attenuation of chronic systemic inflammation (Pan et al. 2018). Taken together, diet and CR may become novel and simple approaches to mitigate age-associated inflammation, promote health and elongate lifespan in humans via modulating the gut microbiota.

Microecological regulators

Microecological regulators such as probiotics, prebiotics, synbiotics, postbiotics and psychobiotics are increasingly gaining importance in preventing and/or reverting the age-related imbalances in the gut microbiota, and conferring healthy anti-aging benefits. Probiotics are defined as live microorganisms that confer a health benefit on the host when administered in adequate amounts. *Bifidobacterium* and *Lactobacillus* strains are the most widely used probiotics in anti-aging research. Prebiotics are selectively fermented ingredients such as inulin-type fructans and galactooligosaccharides that cause specific alterations in the composition or activity of the gut microbiota, generally *Lactobacilli* and *Bifidobacteria*, that confer benefits upon host well-being and health. Synbiotics are a combination of prebiotics and probiotics that may be used to treat a dysfunction of the aging-related gut microbiota. Postbiotics are functional bioactive compounds including microbial cells, cell constituents, and metabolites (SCFAs); they are generated in a matrix during fermentation and may be used to promote health (Wegh et al. 2019). Psychobiotics are defined as live microorganisms (probiotics) that can have health benefits in patients suffering from psychiatric illness when ingested in adequate amounts. This definition has been expanded to any exogenous influence whose effect on the brain is bacterially mediated, which should include probiotics, prebiotics, and even bacterial metabolites (Dinan, Stanton, and Cryan 2013). Psychobiotics can produce neurotransmitters (e.g., γ-aminobutyric acid [GABA] and serotonin) and gasotransmitters (e.g., SCFAs) that exert effects on the gut-brain axis. The main mechanisms underlying their favorable effects on health and longevity include mitigation of age-associated inflammaging, immunosenescence, oxidative stress and gut dysbiosis; improvement of gut mucosal barrier; increased production of neurotransmitters.

The vast majority of studies have shown that probiotics are useful in improving health in elderly subjects by increasing hypocholesterolemic and hypoglycemic effects (Fabersani et al. 2019), and preventing diarrheal diseases (Beausoleil et al. 2007), improving inflammatory disorders (Sharma et al. 2014), and preventing recurring infections (Guillemard et al. 2010), and colon cancer (Sharma and Shukla 2020). Recently, probiotic supplementation has shown promising results in improving the longevity of experimental animals such as *Caenorhabditis elegans* (*C. elegans*). *Clostridium butyricum* MIYAIRI 588 can increase the lifespan and multiple-stress resistance of *C. elegans* through regulating the insulin/IGF-1 signaling pathway and levels of the Nrf2 transcription factor (Kato et al. 2018). The *Lactobacillus fermentum* strain JDFM216 stimulates the longevity and immune response of *C.elegans* through a nuclear hormone receptor

(Park et al. 2018). In addition, killed *Bifidobacterium longum* can enhance stress tolerance and prolong the lifespan of *C. elegans* via DAF-16 (Sugawara and Sakamoto 2018). Sharma et al. evaluated a total of 15 indigenous probiotic strains for their effect on mean life span and demonstrated that feeding with these probiotic cultures is effective in extending the *C. elegans* lifespan (Sharma et al. 2019). A recent study by Zhao et al. demonstrated that *Lactobacillus plantarum* CCFM10 protects against d-galactose-induced oxidative damage and gut dysbiosis in aging mice (Zhao et al. 2018). Several human-origin probiotic strains in combination (mainly *Lactobacillus* and *Enterococcus*) can ameliorate aging-related leaky gut and inflammation, enhance physical function, and increase lifespan via modulating the microbiota-taurine-tight junction axis (Ahmadi et al. 2020). As mentioned above, postbiotics such as SCFAs and polyamines also show life-span enhancing effects, which can improve the gut mucosal barrier and enhance neural microglia maturation, and function (Eisenberg et al. 2016). Smith et al. observed changes in the gut microbiome and fermentation products such as SCFAs concurrent with enhanced longevity in acarbose-treated mice (Smith et al. 2019). Our previous study also found that the psychobiotic strain *Clostridium butyricum* can attenuate microglia-mediated neuroinflammation in AD via regulating the microbiota-gut-brain axis, which is mediated by the metabolite butyrate (Sun et al. 2020). A similar report by Liu et al. showed that butyrate exerts a protective effect against PD in mice through stimulation of GLP-1 (Liu et al. 2017). In addition, our study found that prebiotic fructooligosaccharides exert beneficial effects against AD by regulating the gut microbiota-GLP-1/GLP-1R pathway (Sun, Liu, et al. 2019), which can be considered as novel psychobiotics. Together, the anti-inflammaging, antioxidant, and anti-immunosenescence effects suggest their potential as modulators of healthy aging.

Fecal microbiota transplantation

FMT is defined as the perfusion of treated feces from a healthy donor via the upper or lower gastrointestinal route for microbiota restoration; it was first used by the traditional Chinese medicine doctor Ge hong. Aging is associated with gut dysbiosis, defined as a loss of number and diversity in gut microbiota. Microecological regulators can generally be used for microbiota modulation; however, age-related alterations of the gut microbiota cannot always be restored in this way. FMT can transfer the gut bacteria as a whole or at the species level to correct age-related changes. In fact, gut microbiota composition following FMT is restored to a healthy state similar to the healthy donor. FMT can extend healthspan and lifespan by correcting and decelerating aging-associated gut dysbiosis in progeroid mice, and metabolomic analysis of ileal content indicates that the restoration of secondary bile acids may be a possible mechanism for the beneficial effects of reestablishing a healthy microbiota (Barcena et al. 2019). Chen et al. recently found that transplanting the microbiota from long-living people to mice can reduce aging-related indices and transfers beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, and SCFA-producing genera including *Roseburia*, *Faecalibacterium*, *Ruminococcus* and *Coprococcus*, which indicate that the gut microbiota from long-living people have beneficial effects that promote healthy aging (Chen, Zhang, Zeng, et al. 2020). FMT has also been shown to be effective in treating relapsing or refractory CDI. Luo et al. observed that FMT can improve the cure rate and lower the recurrence rate of CDI in elderly patients (Luo, Tixier, and Grinspan 2020). Clinical and experimental studies reported that FMT may be a promising treatment option for neurological disorders such as AD, PD, stroke, Guillain-Barré syndrome, and others (Vendrik et al. 2020). Our previous animal study demonstrated that FMT can improve cognitive deficits, reduce brain deposition of Aβ, and increase synaptic plasticity by reversing changes of the gut microbiota and SCFAs (Sun, Xu, et al. 2019). Many clinical trials have observed that FMT is sufficient to treat or prevent metabolic disorders (Yu et al. 2020), NAFLD (Craven et al. 2020), T2DM (Kootte et al. 2017), and cancers (Vetizou et al. 2015). Collectively, these studies indicate that FMT can reestablish gut microbiota health and restore the normal function of gut microbiota to anti-inflammaging and anti-immunosenescence, which play vital roles in healthy and successful aging.

Conclusions and perspectives

Given its importance in health and disease, the gut microbiota represents a new avenue in healthy aging studies. During host aging, the gut microbiota undergoes dramatic changes in composition and function; it can shift from eubiosis to dysbiosis, and from commensal to pathogenic, which may occur in the unhealthy aging and lead to the development of various age-related diseases. Although aging is inevitable and irreversible, maintenance of the normal gut microbiota is a potential way to promote healthy aging. Recent studies have achieved great progress elucidating the roles and mechanisms of gut microbiota on aging-associated enteric and extraenteric diseases, and several novel strategies targeting the gut microbiota have been designed to promote human longevity. However, it is still unclear whether gut microbiota alterations are the cause or consequence of aging, and when and how to modulate the gut microbiota to have anti-aging effects remain to be determined. With regard to these issues, it is important to explore the dynamic changes of the gut microbiota with metagenomics and culturomics in large-scale, long-term, longitudinal studies of healthy aging populations (especially the oldest-old) and investigate corresponding alterations in genetics, epigenetics, proteomics, metabolomics, and immunomics with multi-omics techniques. Such studies will establish healthy standard reference datasets that can be used to decipher the relationships between aging microbiota and age-related diseases, and build diagnostic models for these degenerative pathologies and unhealthy aging. However, the healthy standards of the gut microbiota throughout the life cycle are still unclear. There is an urgent need to establish sample banks and corresponding clinical databases including lifestyles, dietary,

physical activities, and antibiotic exposure from large numbers of participants, which will fully consider inter-personal variations. Although age-related gut microbiota changes are quite complicated, comprehensive evaluation of the physiologic and pathologic changes and associated host aging may open up new research perspectives. The newly discovered roles and mechanisms of the gut microbiota in human aging will provide new therapeutic options for targeting the altered gut microbiota. The thought of a microbiota-based intervention to influence human aging and longevity is captivating, although improbable in clinical practice at the present time. Thus, future studies should be designed to better understand the functional associations between the gut microbiota, the aging process and degenerative diseases typical of the elderly, improvement of gut and gut-extraenteric axis aging via modulating the gut microbiota, identification of aging-related functional bacteria or metabolites, and the development of novel microecological regulators for anti-aging. Such studies would help promote healthy and successful aging with gut microbiota-mediated personalized therapies, both in healthy populations and to treat age-related diseases.

Author contributions

Conceptualization: Z.X.L., X.L., and S.C.W. Funding acquisition: Z.X.L., X.L., and S.C.W. Investigation: Z.X.L., X.L., Y.W.C., and X.M.Y. Project administration: Z.X.L. and S.C.W. Supervision: Z.X.L. and S.C.W. Writing-original draft: Z.X.L. and X.L. Writing-review and editing: Z.X.L., X.L. and Y.W.C.

Disclosure statement

The authors declare no conflicts of interest.

Funding

This present work was funded by the grants of the National S&T Major Project of China (2018YFC2000500), the National Natural Science Foundation of China (81771724, 31700800, 81790631), the S&T Major Project of Lishui (2017YSKZ-01 and 2017ZDYF04), Lishui & ZJU Cooperation Project (2018zdhz07), and the Foundation of China's State Key Laboratory for Diagnosis and Treatment of Infectious Diseases.

ORCID

Zongxin Ling http://orcid.org/0000-0001-9662-099X

References

Afolayan, A. O., L. A. Adebusoye, E. O. Cadmus, and F. A. Ayeni. 2020. Insights into the gut microbiota of Nigerian elderly with type 2 diabetes and non-diabetic elderly persons. *Heliyon* 6 (5):e03971. doi: 10.1016/j.heliyon.2020.e03971.

Ahlawat, S., Asha, and K. K. Sharma. 2020. Gut-organ axis: A microbial outreach and networking. *Letters in Applied Microbiology*. doi: 10.1111/lam.13333.

Ahmadi, S., S. Wang, R. Nagpal, B. Wang, S. Jain, A. Razazan, S. P. Mishra, X. Zhu, Z. Wang, K. Kavanagh, et al. 2020. A human-origin probiotic cocktail ameliorates aging-related leaky gut and inflammation via modulating the microbiota/taurine/tight junction axis. *JCI Insight* 5 (9):e132055. doi: 10.1172/jci.insight.132055.

Aho, V. T. E., P. a B. Pereira, S. Voutilainen, L. Paulin, E. Pekkonen, P. Auvinen, and F. Scheperjans. 2019. Gut microbiota in Parkinson's disease: Temporal stability and relations to disease progression. *EBioMedicine* 44:691–707. doi: 10.1016/j.ebiom.2019.05.064.

Al Nabhani, Z., S. Dulauroy, R. Marques, C. Cousu, S. Al Bounny, F. Dejardin, T. Sparwasser, M. Berard, N. Cerf-Bensussan, and G. Eberl. 2019. A weaning reaction to microbiota is required for resistance to immunopathologies in the adult. *Immunity* 50 (5): 1276–88.e5. doi: 10.1016/j.immuni.2019.02.014.

Alkasir, R., J. Li, X. Li, M. Jin, and B. Zhu. 2017. Human gut microbiota: The links with dementia development. *Protein & Cell* 8 (2): 90–102. doi: 10.1007/s13238-016-0338-6.

Alzheimer's Association. 2019. 2019 Alzheimer's disease facts and figures. *Alzheimers Dement* 15 (3):321–87. doi: 10.1016/j.jalz.2019.01.010.

Amsterdam, D., and B. E. Ostrov. 2018. The impact of the microbiome on immunosenescence. *Immunological Investigations* 47 (8):801–11. doi: 10.1080/08820139.2018.1537570.

Arboleya, S., B. Sanchez, G. Solis, N. Fernandez, M. Suarez, A. M. Hernandez-Barranco, C. Milani, A. Margolles, C. G. De Los Reyes-Gavilan, M. Ventura, et al. 2016. Impact of prematurity and perinatal antibiotics on the developing intestinal microbiota: A functional inference study. *International Journal of Molecular Sciences* 17 (5):649. doi: 10.3390/ijms17050649.

Ardissone, A. N., D. M. De La Cruz, A. G. Davis-Richardson, K. T. Rechcigl, N. Li, J. C. Drew, R. Murgas-Torrazza, R. Sharma, M. L. Hudak, E. W. Triplett, et al. 2014. Meconium microbiome analysis identifies bacteria correlated with premature birth. *PLoS One* 9 (3): e90784. doi: 10.1371/journal.pone.0090784.

Arumugam, M., J. Raes, E. Pelletier, D. Le Paslier, T. Yamada, D. R. Mende, G. R. Fernandes, J. Tap, T. Bruls, J. M. Batto, et al. 2011. Enterotypes of the human gut microbiome. *Nature* 473 (7346): 174–80. doi: 10.1038/nature09944.

Asempa, T. E., and D. P. Nicolau. 2017. Clostridium difficile infection in the elderly: An update on management. *Clinical Interventions in Aging* 12:1799–809. doi: 10.2147/CIA.S149089.

Avershina, E., O. Storro, T. Oien, R. Johnsen, P. Pope, and K. Rudi. 2014. Major faecal microbiota shifts in composition and diversity with age in a geographically restricted cohort of mothers and their children. *FEMS Microbiology Ecology* 87 (1):280–90. doi: 10.1111/1574-6941.12223.

Azad, M. B., T. Konya, H. Maughan, D. S. Guttman, C. J. Field, R. S. Chari, M. R. Sears, A. B. Becker, J. A. Scott, A. L. Kozyrskyj, et al. 2013. Gut microbiota of healthy Canadian infants: Profiles by mode of delivery and infant diet at 4 months. *CMAJ: Canadian Medical Association Journal = journal de l'Association medicale canadienne* 185 (5):385–94. doi: 10.1503/cmaj.121189.

Backhed, F., J. Roswall, Y. Peng, Q. Feng, H. Jia, P. Kovatcheva-Datchary, Y. Li, Y. Xia, H. Xie, H. Zhong, et al. 2015. Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host & Microbe* 17 (5):690–703. doi: 10.1016/j.chom.2015.04.004.

Baranowski, B. J., D. M. Marko, R. K. Fenech, A. J. Yang, and R. E. K. Macpherson. 2020. Healthy brain, healthy life: A review of diet and exercise interventions to promote brain health and reduce Alzheimer's disease risk. *Applied Physiology, Nutrition, and Metabolism = Physiologie appliquee, nutrition et metabolisme* 45 (10): 1055–65. doi: 10.1139/apnm-2019-0910.

Barcena, C., R. Valdes-Mas, P. Mayoral, C. Garabaya, S. Durand, F. Rodriguez, M. T. Fernandez-Garcia, N. Salazar, A. M. Nogacka, N. Garatachea, et al. 2019. Healthspan and lifespan extension by fecal microbiota transplantation into progeroid mice. *Nature Medicine* 25 (8):1234–42. doi: 10.1038/s41591-019-0504-5.

Barnes, M. J., and F. Powrie. 2011. Immunology. The gut's Clostridium cocktail. *Science (New York, N.Y.)* 331 (6015):289–90. doi: 10.1126/science.1201291.

Barrea, L., G. Pugliese, D. Laudisio, A. Colao, S. Savastano, and G. Muscogiuri. 2020. Mediterranean diet as medical prescription in menopausal women with obesity: A practical guide for nutritionists. *Critical Reviews in Food Science and Nutrition*. doi: 10.1080/10408398.2020.1755220.

Bastin, M., and F. Andreelli. 2020. The gut microbiota and diabetic cardiomyopathy in humans. *Diabetes & Metabolism* 46 (3):197–202. doi: 10.1016/j.diabet.2019.10.003.

Bauernfeind, F., S. Niepmann, P. A. Knolle, and V. Hornung. 2016. Aging-associated TNF production primes Inflammasome activation and NLRP3-related metabolic disturbances. *Journal of Immunology (Baltimore, Md.: 1950)* 197 (7):2900–8. doi: 10.4049/jimmunol.1501336.

Beausoleil, M., N. Fortier, S. Guenette, A. L'ecuyer, M. Savoie, M. Franco, J. Lachaine, and K. Weiss. 2007. Effect of a fermented milk combining Lactobacillus acidophilus Cl1285 and Lactobacillus casei in the prevention of antibiotic-associated diarrhea: A randomized, double-blind, placebo-controlled trial. *Canadian Journal of Gastroenterology = Journal Canadien de Gastroenterologie* 21 (11):732–6. doi: 10.1155/2007/720205.

Benítez-Páez, A., M. Olivares, H. Szajewska, M. Pieścik-Lech, I. Polanco, G. Castillejo, M. Nuñez, C. Ribes-Koninckx, I. R. Korponay-Szabó, S. Koletzko, et al. 2020. Breast-milk microbiota linked to celiac disease development in children: A pilot study from the prevent CD cohort. *Frontiers in Microbiology* 11:1335. doi: 10.3389/fmicb.2020.01335.

Biagi, E., M. Candela, S. Turroni, P. Garagnani, C. Franceschi, and P. Brigidi. 2013. Ageing and gut microbes: Perspectives for health maintenance and longevity. *Pharmacological Research* 69 (1):11–20. doi: 10.1016/j.phrs.2012.10.005.

Biagi, E., C. Franceschi, S. Rampelli, M. Severgnini, R. Ostan, S. Turroni, C. Consolandi, S. Quercia, M. Scurti, D. Monti, et al. 2016. Gut microbiota and extreme longevity. *Current Biology: CB* 26 (11):1480–5. doi: 10.1016/j.cub.2016.04.016.

Biagi, E., L. Nylund, M. Candela, R. Ostan, L. Bucci, E. Pini, J. Nikkila, D. Monti, R. Satokari, C. Franceschi, et al. 2010. Through ageing, and beyond: Gut microbiota and inflammatory status in seniors and centenarians. *PLoS One* 5 (5):e10667. doi: 10.1371/journal.pone.0010667.

Bode, L. 2012. Human milk oligosaccharides: Every baby needs a sugar mama. *Glycobiology* 22 (9):1147–62. doi: 10.1093/glycob/cws074.

Bokulich, N. A., J. Chung, T. Battaglia, N. Henderson, M. Jay, H. Li, A. D. Lieber, F. Wu, G. I. Perez-Perez, Y. Chen, et al. 2016. Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Science Translational Medicine* 8 (343):343ra382. doi: 10.1126/scitranslmed.aad7121.

Bonciani, D., A. Verdelli, V. Bonciolini, A. D'errico, E. Antiga, P. Fabbri, and M. Caproni. 2012. Dermatitis herpetiformis: From the genetics to the development of skin lesions. *Clinical & Developmental Immunology* 2012:239691. doi: 10.1155/2012/239691.

Bonte, F., D. Girard, J. C. Archambault, and A. Desmouliere. 2019. Skin changes during ageing. *Sub-cellular Biochemistry* 91:249–80. doi: 10.1007/978-981-13-3681-2_10.

Boursier, J., O. Mueller, M. Barret, M. Machado, L. Fizanne, F. Araujo-Perez, C. D. Guy, P. C. Seed, J. F. Rawls, L. A. David, et al. 2016. The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota. *Hepatology (Baltimore, Md.)* 63 (3):764–75. doi: 10.1002/hep.28356.

Britton, R. A., R. Irwin, D. Quach, L. Schaefer, J. Zhang, T. Lee, N. Parameswaran, and L. R. Mccabe. 2014. Probiotic L. reuteri treatment prevents bone loss in a menopausal ovariectomized mouse model. *Journal of Cellular Physiology* 229 (11):1822–30. doi: 10.1002/jcp.24636.

Brook, I. 1996. Veillonella infections in children. *Journal of Clinical Microbiology* 34 (5):1283–5. doi: 10.1128/JCM.34.5.1283-1285.1996.

Brooks-Wilson, A. R. 2013. Genetics of healthy aging and longevity. *Human Genetics* 132 (12):1323–38. doi: 10.1007/s00439-013-1342-z.

Cantley, M. D., D. P. Fairlie, P. M. Bartold, K. D. Rainsford, G. T. Le, A. J. Lucke, C. A. Holding, and D. R. Haynes. 2011. Inhibitors of histone deacetylases in class I and class II suppress human osteoclasts in vitro. *Journal of Cellular Physiology* 226 (12):3233–41. doi: 10.1002/jcp.22684.

Caporaso, J. G., C. L. Lauber, E. K. Costello, D. Berg-Lyons, A. Gonzalez, J. Stombaugh, D. Knights, P. Gajer, J. Ravel, N. Fierer, et al. 2011. Moving pictures of the human microbiome. *Genome Biology* 12 (5):R50. doi: 10.1186/gb-2011-12-5-r50.

Cariello, M., A. Contursi, R. M. Gadaleta, E. Piccinin, S. De Santis, M. Piglionica, A. F. Spaziante, C. Sabba, G. Villani, and A. Moschetta. 2020. Extra-virgin olive oil from apulian cultivars and intestinal inflammation. *Nutrients* 12 (4):1084. doi: 10.3390/nu12041084.

Castaneda-Delgado, J. E., I. Frausto-Lujan, I. Gonzalez-Curiel, A. Montoya-Rosales, C. J. Serrano, F. Torres-Juarez, J. A. Enciso-Moreno, and B. Rivas-Santiago. 2017. Differences in cytokine production during aging and its relationship with antimicrobial peptides production. *Immunological Investigations* 46 (1):48–58. doi: 10.1080/08820139.2016.1212873.

Cattaneo, A., N. Cattane, S. Galluzzi, S. Provasi, N. Lopizzo, C. Festari, C. Ferrari, U. P. Guerra, B. Paghera, C. Muscio, et al. 2017. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiology of Aging* 49:60–8. doi: 10.1016/j.neurobiolaging.2016.08.019.

Celaj, S., M. W. Gleeson, J. Deng, G. A. O'toole, T. H. Hampton, M. F. Toft, H. G. Morrison, M. L. Sogin, J. Putra, A. A. Suriawinata, et al. 2014. The microbiota regulates susceptibility to Fas-mediated acute hepatic injury. *Laboratory Investigation; a Journal of Technical Methods and Pathology* 94 (9):938–49. doi: 10.1038/labinvest.2014.93.

Chaari, A. 2020. Inhibition of human islet amyloid polypeptide aggregation and cellular toxicity by oleuropein and derivatives from olive oil. *International Journal of Biological Macromolecules* 162:284–300. doi: 10.1016/j.ijbiomac.2020.06.170.

Chen, C. N., Y. H. Liao, S. C. Tsai, and L. V. Thompson. 2019. Age-dependent effects of caloric restriction on mTOR and ubiquitin-proteasome pathways in skeletal muscles. *Geroscience* 41 (6):871–80. doi: 10.1007/s11357-019-00109-8.

Chen, M. L., K. Takeda, and M. S. Sundrud. 2019. Emerging roles of bile acids in mucosal immunity and inflammation. *Mucosal Immunology* 12 (4):851–61. doi: 10.1038/s41385-019-0162-4.

Chen, W., F. Liu, Z. Ling, X. Tong, and C. Xiang. 2012. Human intestinal lumen and mucosa-associated microbiota in patients with colorectal cancer. *PLoS One* 7 (6):e39743. doi: 10.1371/journal.pone.0039743.

Chen, W., S. Zhang, J. Wu, T. Ye, S. Wang, P. Wang, and D. Xing. 2020. Butyrate-producing bacteria and the gut-heart axis in atherosclerosis. *Clinica Chimica Acta* 507:236–41. doi: 10.1016/j.cca.2020.04.037.

Chen, Y., S. Zhang, B. Zeng, J. Zhao, M. Yang, M. Zhang, Y. Li, Q. Ni, D. Wu, and Y. Li. 2020. Transplant of microbiota from long-living people to mice reduces aging-related indices and transfers beneficial bacteria. *Aging* 12 (6):4778–93. doi: 10.18632/aging.102872.

Cho, S. Y., J. Kim, J. H. Lee, J. H. Sim, D. H. Cho, I. H. Bae, H. Lee, M. A. Seol, H. M. Shin, T. J. Kim, et al. 2016. Modulation of gut microbiota and delayed immunosenescence as a result of syringaresinol consumption in middle-aged mice. *Scientific Reports* 6:39026. doi: 10.1038/srep39026.

Claesson, M. J., S. Cusack, O. O'sullivan, R. Greene-Diniz, H. De Weerd, E. Flannery, J. R. Marchesi, D. Falush, T. Dinan, G. Fitzgerald, et al. 2011. Composition, variability, and temporal stability of the intestinal microbiota of the elderly. *Proceedings of the National Academy of Sciences of the United States of America* 108 (Supplement_1):4586–91. doi: 10.1073/pnas.1000097107.

Claesson, M. J., I. B. Jeffery, S. Conde, S. E. Power, E. M. O'connor, S. Cusack, H. M. Harris, M. Coakley, B. Lakshminarayanan, O. O'sullivan, et al. 2012. Gut microbiota composition correlates with diet and health in the elderly. *Nature* 488 (7410):178–84. doi: 10.1038/nature11319.

Clark, R. I., A. Salazar, R. Yamada, S. Fitz-Gibbon, M. Morselli, J. Alcaraz, A. Rana, M. Rera, M. Pellegrini, W. W. Ja, et al. 2015. Distinct shifts in microbiota composition during drosophila aging impair intestinal function and drive mortality. *Cell Reports* 12 (10): 1656–67. doi: 10.1016/j.celrep.2015.08.004.

Clements, S. J., and S. R. Carding. 2018. Diet, the intestinal microbiota, and immune health in aging. *Critical Reviews in Food Science and Nutrition* 58 (4):651–61. doi: 10.1080/10408398.2016.1211086.

Collado, M. C., S. Rautava, J. Aakko, E. Isolauri, and S. Salminen. 2016. Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. *Scientific Reports* 6:23129. doi: 10.1038/srep23129.

Collino, S., I. Montoliu, F. P. Martin, M. Scherer, D. Mari, S. Salvioli, L. Bucci, R. Ostan, D. Monti, E. Biagi, et al. 2013. Metabolic signatures of extreme longevity in northern Italian centenarians reveal a complex remodeling of lipids, amino acids, and gut microbiota metabolism. *PLoS One* 8 (3):e56564. doi: 10.1371/journal.pone.0056564.

Cong, X., W. Xu, S. Janton, W. A. Henderson, A. Matson, J. M. Mcgrath, K. Maas, and J. Graf. 2016. Gut microbiome developmental patterns in early life of preterm infants: Impacts of feeding and gender. *PLoS One* 11 (4):e0152751. doi: 10.1371/journal.pone.0152751.

Corina, A., M. B. Abrudan, D. Nikolic, A. F. Cătoi, R. Chianetta, G. Castellino, R. Citarrella, A. P. Stoian, P. Pérez-Martínez, and M. Rizzo. 2019. Effects of aging and diet on cardioprotection and cardiometabolic risk markers. *Current Pharmaceutical Design* 25 (35): 3704–14. doi: 10.2174/1381612825666191105111232.

Costea, P. I., F. Hildebrand, M. Arumugam, F. Backhed, M. J. Blaser, F. D. Bushman, W. M. De Vos, S. D. Ehrlich, C. M. Fraser, M. Hattori, et al. 2018. Enterotypes in the landscape of gut microbial community composition. *Nature Microbiology* 3 (1):8–16. doi: 10.1038/s41564-017-0072-8.

Craven, L., A. Rahman, S. Nair Parvathy, M. Beaton, J. Silverman, K. Qumosani, I. Hramiak, R. Hegele, T. Joy, J. Meddings, et al. 2020. Allogenic fecal microbiota transplantation in patients with nonalcoholic fatty liver disease improves abnormal small intestinal permeability: A randomized control trial. *The American Journal of Gastroenterology* 115 (7):1055–65. doi: 10.14309/ajg.0000000000000661.

Cryan, J. F., K. J. O'riordan, C. S. M. Cowan, K. V. Sandhu, T. F. S. Bastiaanssen, M. Boehme, M. G. Codagnone, S. Cussotto, C. Fulling, A. V. Golubeva, et al. 2019. The microbiota-gut-brain axis. *Physiological Reviews* 99 (4):1877–2013. doi: 10.1152/physrev.00018.2018.

Dato, S., G. Rose, P. Crocco, D. Monti, P. Garagnani, C. Franceschi, and G. Passarino. 2017. The genetics of human longevity: An intricacy of genes, environment, culture and microbiome. *Mechanisms of Ageing and Development* 165 (Pt B):147–55. doi: 10.1016/j.mad.2017.03.011.

De Sire, R., G. Rizzatti, F. Ingravalle, M. Pizzoferrato, V. Petito, L. Lopetuso, C. Graziani, A. De Sire, M. C. Mentella, M. C. Mele, et al. 2018. Skeletal muscle-gut axis: Emerging mechanisms of sarcopenia for intestinal and extra intestinal diseases. *Minerva Gastroenterologica e Dietologica* 64 (4):351–62. doi: 10.23736/S1121-421x.18.02511-4.

Dehoux, P., J. C. Marvaud, A. Abouelleil, A. M. Earl, T. Lambert, and C. Dauga. 2016. Comparative genomics of Clostridium bolteae and Clostridium clostridioforme reveals species-specific genomic properties and numerous putative antibiotic resistance determinants. *BMC Genomics* 17 (1):819. doi: 10.1186/s12864-016-3152-x.

Dejong, E. N., M. G. Surette, and D. M. E. Bowdish. 2020. The Gut Microbiota and Unhealthy Aging: Disentangling Cause from Consequence. *Cell Host & Microbe* 28 (2):180–9. doi: 10.1016/j.chom.2020.07.013.

Derrien, M., A. S. Alvarez, and W. M. De Vos. 2019. The gut microbiota in the first decade of life. *Trends in Microbiology* 27 (12): 997–1010. doi: 10.1016/j.tim.2019.08.001.

Dhouafli, Z., K. Cuanalo-Contreras, E. A. Hayouni, C. E. Mays, C. Soto, and I. Moreno-Gonzalez. 2018. Inhibition of protein misfolding and aggregation by natural phenolic compounds. *Cellular and Molecular Life Sciences: CMLS* 75 (19):3521–38. doi: 10.1007/s00018-018-2872-2.

Di Serio, M. G., L. Di Giacinto, G. Di Loreto, L. Giansante, M. Pellegrino, R. Vito, and E. Perri. 2016. Chemical and sensory characteristics of Italian virgin olive oils from Grossa di Gerace cv. *European Journal of Lipid Science and Technology* 118 (2):288–98. doi: 10.1002/ejlt.201400622.

Differding, M. K., S. E. Benjamin-Neelon, C. Hoyo, T. Ostbye, and N. T. Mueller. 2020. Timing of complementary feeding is associated with gut microbiota diversity and composition and short chain fatty acid concentrations over the first year of life. *BMC Microbiology* 20 (1):56. doi: 10.1186/s12866-020-01723-9.

Dinan, T. G., C. Stanton, and J. F. Cryan. 2013. Psychobiotics: A novel class of psychotropic. *Biological Psychiatry* 74 (10):720–6. doi: 10.1016/j.biopsych.2013.05.001.

Dominguez-Bello, M. G., E. K. Costello, M. Contreras, M. Magris, G. Hidalgo, N. Fierer, and R. Knight. 2010. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proceedings of the National Academy of Sciences of the United States of America* 107 (26):11971–5. doi: 10.1073/pnas.1002601107.

Dominguez-Bello, M. G., K. M. De Jesus-Laboy, N. Shen, L. M. Cox, A. Amir, A. Gonzalez, N. A. Bokulich, S. J. Song, M. Hoashi, J. I. Rivera-Vinas, et al. 2016. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nature Medicine* 22 (3):250–3. doi: 10.1038/nm.4039.

Eisenberg, T., M. Abdellatif, S. Schroeder, U. Primessnig, S. Stekovic, T. Pendl, A. Harger, J. Schipke, A. Zimmermann, A. Schmidt, et al. 2016. Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nature Medicine* 22 (12):1428–38. doi: 10.1038/nm.4222.

Emoto, T., T. Yamashita, T. Kobayashi, N. Sasaki, Y. Hirota, T. Hayashi, A. So, K. Kasahara, K. Yodoi, T. Matsumoto, et al. 2017. Characterization of gut microbiota profiles in coronary artery disease patients using data mining analysis of terminal restriction fragment length polymorphism: Gut microbiota could be a diagnostic marker of coronary artery disease. *Heart and Vessels* 32 (1):39–46. doi: 10.1007/s00380-016-0841-y.

Emoto, T., T. Yamashita, N. Sasaki, Y. Hirota, T. Hayashi, A. So, K. Kasahara, K. Yodoi, T. Matsumoto, T. Mizoguchi, et al. 2016. Analysis of gut microbiota in coronary artery disease patients: A possible link between gut microbiota and coronary artery disease. *Journal of Atherosclerosis and Thrombosis* 23 (8):908–21. doi: 10.5551/jat.32672.

Erny, D., A. L. Hrabě de Angelis, D. Jaitin, P. Wieghofer, O. Staszewski, E. David, H. Keren-Shaul, T. Mahlakoiv, K. Jakobshagen, T. Buch, et al. 2015. Host microbiota constantly control maturation and function of microglia in the CNS. *Nature Neuroscience* 18 (7): 965–77. doi: 10.1038/nn.4030.

Escobar, M. F., M. A. Hincapie, and J. S. Barona. 2020. Immunological role of the maternal uterine microbiota in postpartum hemorrhage. *Frontiers in Immunology* 11:504. doi: 10.3389/fimmu.2020.00504.

Fabbiano, S., N. Suarez-Zamorano, C. Chevalier, V. Lazarevic, S. Kieser, D. Rigo, S. Leo, C. Veyrat-Durebex, N. Gaia, M. Maresca, et al. 2018. Functional gut microbiota remodeling contributes to the caloric restriction-induced metabolic improvements. *Cell Metabolism* 28 (6):907–21.e7. doi: 10.1016/j.cmet.2018.08.005.

Fabersani, E., M. Russo, A. Marquez, C. Abeijon-Mukdsi, R. Medina, and P. Gauffin-Cano. 2019. Modulation of intestinal microbiota and immunometabolic parameters by caloric restriction and lactic acid bacteria. *Food Research International (Ottawa, Ont.)* 124:188–99. doi: 10.1016/j.foodres.2018.06.014.

Fahlstrom, A., Q. Yu, and B. Ulfhake. 2011. Behavioral changes in aging female C57BL/6 mice. *Neurobiology of Aging* 32 (10):1868–80. doi: 10.1016/j.neurobiolaging.2009.11.003.

Fallani, M., S. Amarri, A. Uusijarvi, R. Adam, S. Khanna, M. Aguilera, A. Gil, J. M. Vieites, E. Norin, D. Young, et al. 2011. Determinants of the human infant intestinal microbiota after the introduction of first complementary foods in infant samples from five European

centres. *Microbiology* 157 (Pt 5):1385–92. doi: 10.1099/mic.0.042143-0.

Fang, E. F., M. Scheibye-Knudsen, H. J. Jahn, J. Li, L. Ling, H. W. Guo, X. Q. Zhu, V. Preedy, H. M. Lu, V. A. Bohr, et al. 2015. A research agenda for aging in China in the 21st century. *Ageing Research Reviews* 24 (Pt B):197–205. doi: 10.1016/j.arr.2015.08.003.

Ferri, C. P., M. Prince, C. Brayne, H. Brodaty, L. Fratiglioni, M. Ganguli, K. Hall, K. Hasegawa, H. Hendrie, Y. Huang, et al. 2005. Global prevalence of dementia: A Delphi consensus study. *Lancet (London, England)* 366 (9503):2112–7. doi: 10.1016/S0140-6736(05)67889-0.

Fluitman, K. S., M. Wijdeveld, M. Nieuwdorp, and R. G. IJzerman. 2018. Potential of butyrate to influence food intake in mice and men. *Gut* 67 (7):1203–4. doi: 10.1136/gutjnl-2017-315543.

Forsgren, M., E. Isolauri, S. Salminen, and S. Rautava. 2017. Late preterm birth has direct and indirect effects on infant gut microbiota development during the first six months of life. *Acta Paediatrica (Oslo, Norway: 1992)* 106 (7):1103–9. doi: 10.1111/apa.13837.

Foscolou, A., N. M. D'Cunha, N. Naumovski, S. Tyrovolas, C. Chrysohoou, L. Rallidis, E. Polychronopoulos, A.-L. Matalas, L. S. Sidossis, and D. Panagiotakos. 2020. The association between the level of adherence to the Mediterranean diet and successful aging: An analysis of the ATTICA and MEDIS (MEDiterranean Islands Study) epidemiological studies. *Archives of Gerontology and Geriatrics* 89:104044. doi: 10.1016/j.archger.2020.104044.

Franceschi, C., M. Bonafe, S. Valensin, F. Olivieri, M. De Luca, E. Ottaviani, and G. De Benedictis. 2000. Inflamm-aging. An evolutionary perspective on immunosenescence. *Annals of the New York Academy of Sciences* 908:244–54. doi: 10.1111/j.1749-6632.2000.tb06651.x.

Franceschi, C., M. Capri, D. Monti, S. Giunta, F. Olivieri, F. Sevini, M. P. Panourgia, L. Invidia, L. Celani, M. Scurti, et al. 2007. Inflammaging and anti-inflammaging: A systemic perspective on aging and longevity emerged from studies in humans. *Mechanisms of Ageing and Development* 128 (1):92–105. doi: 10.1016/j.mad.2006.11.016.

Franceschi, C., P. Garagnani, P. Parini, C. Giuliani, and A. Santoro. 2018. Inflammaging: A new immune-metabolic viewpoint for age-related diseases. *Nature Reviews. Endocrinology* 14 (10):576–90. doi: 10.1038/s41574-018-0059-4.

Franceschi, C., P. Garagnani, G. Vitale, M. Capri, and S. Salvioli. 2017. Inflammaging and 'Garb-aging'. *Trends in Endocrinology and Metabolism: TEM* 28 (3):199–212. doi: 10.1016/j.tem.2016.09.005.

Fransen, F., A. A. Van Beek, T. Borghuis, S. E. Aidy, F. Hugenholtz, C. Van Der Gaast-De Jongh, H. F. J. Savelkoul, M. I. De Jonge, M. V. Boekschoten, H. Smidt, et al. 2017. Aged gut microbiota contributes to systemical inflammaging after transfer to germ-free mice. *Frontiers in Immunology* 8:1385. doi: 10.3389/fimmu.2017.01385.

Fries, J. F. 1980. Aging, natural death, and the compression of morbidity. *The New England Journal of Medicine* 303 (3):130–5. doi: 10.1056/NEJM198007173030304.

Fulop, T., A. Larbi, G. Dupuis, A. Le Page, E. H. Frost, A. A. Cohen, J. M. Witkowski, and C. Franceschi. 2018. Immunosenescence and inflamm-aging as two sides of the same coin: Friends or foes? *Frontiers in Immunology* 8:1960. doi: 10.3389/Fimmu.2017.01960.

Galkin, F., P. Mamoshina, A. Aliper, E. Putin, V. Moskalev, V. N. Gladyshev, and A. Zhavoronkov. 2020. Human gut microbiome aging clock based on taxonomic profiling and deep learning. *iScience* 23 (6):101199. doi: 10.1016/j.isci.2020.101199.

Ganal-Vonarburg, S. C., M. W. Hornef, and A. J. Macpherson. 2020. Microbial-host molecular exchange and its functional consequences in early mammalian life. *Science (New York, N.Y.)* 368 (6491):604–7. doi: 10.1126/science.aba0478.

Gao, H. M., F. Zhang, H. Zhou, W. Kam, B. Wilson, and J. S. Hong. 2011. Neuroinflammation and α-synuclein dysfunction potentiate each other, driving chronic progression of neurodegeneration in a mouse model of Parkinson's disease. *Environmental Health Perspectives* 119 (6):807–14. doi: 10.1289/ehp.1003013.

Gensollen, T., S. S. Iyer, D. L. Kasper, and R. S. Blumberg. 2016. How colonization by microbiota in early life shapes the immune system. *Science (New York, N.Y.)* 352 (6285):539–44. doi: 10.1126/science.aad9378.

Ghosh, T. S., S. Rampelli, I. B. Jeffery, A. Santoro, M. Neto, M. Capri, E. Giampieri, A. Jennings, M. Candela, S. Turroni, et al. 2020. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: The NU-AGE 1-year dietary intervention across five European countries. *Gut* 69 (7):1218–28. doi: 10.1136/gutjnl-2019-319654.

Gibson, M. K., T. S. Crofts, and G. Dantas. 2015. Antibiotics and the developing infant gut microbiota and resistome. *Current Opinion in Microbiology* 27:51–6. doi: 10.1016/j.mib.2015.07.007.

Gibson, M. K., B. Wang, S. Ahmadi, C. A. Burnham, P. I. Tarr, B. B. Warner, and G. Dantas. 2016. Developmental dynamics of the preterm infant gut microbiota and antibiotic resistome. *Nature Microbiology* 1:16024. doi: 10.1038/nmicrobiol.2016.24.

Gollwitzer, E. S., and B. J. Marsland. 2015. Impact of early-life exposures on immune maturation and susceptibility to disease. *Trends in Immunology* 36 (11):684–96. doi: 10.1016/j.it.2015.09.009.

Govindaraju, D., G. Atzmon, and N. Barzilai. 2015. Genetics, lifestyle and longevity: Lessons from centenarians. *Applied & Translational Genomics* 4:23–32. doi: 10.1016/j.atg.2015.01.001.

Goyal, A., V. Dubinkina, and S. Maslov. 2018. Multiple stable states in microbial communities explained by the stable marriage problem. *The ISME Journal* 12 (12):2823–34. doi: 10.1038/s41396-018-0222-x.

Granic, A., A. A. Sayer, and S. M. Robinson. 2019. Dietary patterns, skeletal muscle health, and sarcopenia in older adults. *Nutrients* 11 (4):745. doi: 10.3390/nu11040745.

Grosicki, G. J., R. A. Fielding, and M. S. Lustgarten. 2018. Gut microbiota contribute to age-related changes in skeletal muscle size, composition, and function: Biological basis for a gut-muscle axis. *Calcified Tissue International* 102 (4):433–42. doi: 10.1007/s00223-017-0345-5.

Gu, S. L., Y. B. Chen, X. W. Zhang, H. F. Lu, T. Lv, P. Shen, L. X. Lv, B. W. Zheng, X. W. Jiang, and L. J. Li. 2016. Identification of key taxa that favor intestinal colonization of Clostridium difficile in an adult Chinese population. *Microbes and Infection* 18 (1):30–8. doi: 10.1016/j.micinf.2015.09.008.

Guedj, A., Y. Volman, A. Geiger-Maor, J. Bolik, N. Schumacher, S. Kunzel, J. F. Baines, Y. Nevo, S. Elgavish, E. Galun, et al. 2020. Gut microbiota shape 'inflamm-ageing' cytokines and account for age-dependent decline in DNA damage repair. *Gut* 69 (6):1064–75. doi: 10.1136/gutjnl-2019-318491.

Gueniche, A., D. Philippe, P. Bastien, G. Reuteler, S. Blum, I. Castiel-Higounenc, L. Breton, and J. Benyacoub. 2014. Randomised double-blind placebo-controlled study of the effect of Lactobacillus paracasei NCC 2461 on skin reactivity. *Beneficial Microbes* 5 (2):137–45. doi: 10.3920/BM2013.0001.

Guillemard, E., F. Tondu, F. Lacoin, and J. Schrezenmeir. 2010. Consumption of a fermented dairy product containing the probiotic Lactobacillus casei DN-114001 reduces the duration of respiratory infections in the elderly in a randomised controlled trial. *British Journal of Nutrition* 103 (1):58–68. doi: 10.1017/S0007114509991395.

Hamady, M., J. J. Walker, J. K. Harris, N. J. Gold, and R. Knight. 2008. Error-correcting barcoded primers for pyrosequencing hundreds of samples in multiplex. *Nature Methods* 5 (3):235–7. doi: 10.1038/nmeth.1184.

Haran, J. P., S. K. Bhattarai, S. E. Foley, P. Dutta, D. V. Ward, V. Bucci, and B. A. Mccormick. 2019. Alzheimer's disease microbiome is associated with dysregulation of the anti-inflammatory p-glycoprotein pathway. *mBio* 10 (3):e00632-19. doi: 10.1128/mBio.00632-19.

Hermansson, H., H. Kumar, M. C. Collado, S. Salminen, E. Isolauri, and S. Rautava. 2019. Breast milk microbiota is shaped by mode of delivery and intrapartum antibiotic exposure. *Frontiers in Nutrition* 6:4. doi: 10.3389/Fnut.2019.00004.

Hesla, H. M., F. Stenius, L. Jaderlund, R. Nelson, L. Engstrand, J. Alm, and J. Dicksved. 2014. Impact of lifestyle on the gut microbiota of healthy infants and their mothers—The ALADDIN birth cohort. *FEMS Microbiology Ecology* 90 (3):791–801. doi: 10.1111/1574-6941.12434.

Hill, C. J., D. B. Lynch, K. Murphy, M. Ulaszewska, I. B. Jeffery, C. A. O'shea, C. Watkins, E. Dempsey, F. Mattivi, K. Tuohy, et al. 2017. Evolution of gut microbiota composition from birth to 24 weeks in the INFANTMET Cohort. *Microbiome* 5 (1):21. doi: 10.1186/s40168-016-0213-y.

Hill-Burns, E. M., J. W. Debelius, J. T. Morton, W. T. Wissemann, M. R. Lewis, Z. D. Wallen, S. D. Peddada, S. A. Factor, E. Molho, C. P. Zabetian, et al. 2017. Parkinson's disease and Parkinson's disease medications have distinct signatures of the gut microbiome. *Movement Disorders* 32 (5):739–49. doi: 10.1002/mds.26942.

Ho, N. T., F. Li, K. A. Lee-Sarwar, H. M. Tun, B. P. Brown, P. S. Pannaraj, J. M. Bender, M. B. Azad, A. L. Thompson, S. T. Weiss, et al. 2018. Meta-analysis of effects of exclusive breastfeeding on infant gut microbiota across populations. *Nature Communications* 9 (1):4169. doi: 10.1038/s41467-018-06473-x.

Jackson, M. A., M. Jackson, I. B. Jeffery, M. Beaumont, J. T. Bell, A. G. Clark, R. E. Ley, P. W. O'Toole, T. D. Spector, and C. J. Steves. 2016. Signatures of early frailty in the gut microbiota. *Genome Medicine* 8 (1):8. doi: 10.1186/s13073-016-0262-7.

Jenner, P. 2008. Molecular mechanisms of L-DOPA-induced dyskinesia. *Nature Reviews. Neuroscience* 9 (9):665–77. doi: 10.1038/nrn2471.

Jennings, A., S. C. Cunnane, and A. M. Minihane. 2020. Can nutrition support healthy cognitive ageing and reduce dementia risk? *BMJ (Clinical Research ed.)* 369:M2269. doi: 10.1136/Bmj.M2269.

Jeong, J. J., K. A. Kim, Y. J. Hwang, M. J. Han, and D. H. Kim. 2016. Anti-inflammaging effects of Lactobacillus brevis OW38 in aged mice. *Beneficial Microbes* 7 (5):707–18. doi: 10.3920/BM2016.0016.

Jie, Z., H. Xia, S. L. Zhong, Q. Feng, S. Li, S. Liang, H. Zhong, Z. Liu, Y. Gao, H. Zhao, et al. 2017. The gut microbiome in atherosclerotic cardiovascular disease. *Nature Communications* 8 (1):845. doi: 10.1038/s41467-017-00900-1.

Karlsson, F. H., V. Tremaroli, I. Nookaew, G. Bergstrom, C. J. Behre, B. Fagerberg, J. Nielsen, and F. Backhed. 2013. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature* 498 (7452):99–103. doi: 10.1038/nature12198.

Kato, M., Y. Hamazaki, S. Sun, Y. Nishikawa, and E. Kage-Nakadai. 2018. Clostridium butyricum MIYAIRI 588 increases the lifespan and multiple-stress resistance of Caenorhabditis elegans. *Nutrients* 10 (12):1921. doi: 10.3390/nu10121921.

Ke, K., M. Arra, and Y. Abu-Amer. 2019. Mechanisms underlying bone loss associated with gut inflammation. *International Journal of Molecular Sciences* 20 (24):6323. doi: 10.3390/ijms20246323.

Khine, W. W. T., E. S. Rahayu, T. Y. See, S. Kuah, S. Salminen, J. Nakayama, and Y. K. Lee. 2020. Indonesian children fecal microbiome from birth until weaning was different from microbiomes of their mothers. *Gut Microbes* 12 (1):1761240–19. doi: 10.1080/19490976.2020.1761240.

Kim, H. B., K. Borewicz, B. A. White, R. S. Singer, S. Sreevatsan, Z. J. Tu, and R. E. Isaacson. 2011. Longitudinal investigation of the age-related bacterial diversity in the feces of commercial pigs. *Veterinary Microbiology* 153 (1-2):124–33. doi: 10.1016/j.vetmic.2011.05.021.

Kim, K. A., J. J. Jeong, S. Y. Yoo, and D. H. Kim. 2016. Gut microbiota lipopolysaccharide accelerates inflamm-aging in mice. *BMC Microbiology* 16:9. doi: 10.1186/s12866-016-0625-7.

Kim, S., and S. M. Jazwinski. 2018. The gut microbiota and healthy aging: A mini-review. *Gerontology* 64 (6):513–20. doi: 10.1159/000490615.

Koenig, J. E., A. Spor, N. Scalfone, A. D. Fricker, J. Stombaugh, R. Knight, L. T. Angenent, and R. E. Ley. 2011. Succession of microbial consortia in the developing infant gut microbiome. *Proceedings of the National Academy of Sciences of the United States of America* 108 Suppl 1 (Suppl 1):4578–85. doi: 10.1073/pnas.1000081107.

Kootte, R. S., E. Levin, J. Salojarvi, L. P. Smits, A. V. Hartstra, S. D. Udayappan, G. Hermes, K. E. Bouter, A. M. Koopen, J. J. Holst, et al. 2017. Improvement of insulin sensitivity after lean donor feces in metabolic syndrome is driven by baseline intestinal microbiota composition. *Cell Metabolism* 26 (4):611–9.e6. doi: 10.1016/j.cmet.2017.09.008.

Koren, O., A. Spor, J. Felin, F. Fak, J. Stombaugh, V. Tremaroli, C. J. Behre, R. Knight, B. Fagerberg, R. E. Ley, et al. 2011. Human oral, gut, and plaque microbiota in patients with atherosclerosis. *Proceedings of the National Academy of Sciences of the United States of America* 108 (Suppl 1):4592–8. doi: 10.1073/pnas.1011383107.

Korpela, K., E. W. Blakstad, S. J. Moltu, K. Strømmen, B. Nakstad, A. E. Rønnestad, K. Braekke, P. O. Iversen, C. A. Drevon, and W. de Vos. 2018. Intestinal microbiota development and gestational age in preterm neonates. *Scientific Reports* 8 (1):2453. doi: 10.1038/s41598-018-20827-x.

Kovatcheva-Datchary, P., A. Nilsson, R. Akrami, Y. S. Lee, F. De Vadder, T. Arora, A. Hallen, E. Martens, I. Björck, and F. Bäckhed. 2015. Dietary fiber-induced improvement in glucose metabolism is associated with increased abundance of Prevotella. *Cell Metabolism* 22 (6):971–82. doi: 10.1016/j.cmet.2015.10.001.

Ku, H. J., Y. T. Kim, and J. H. Lee. 2020. Microbiome study of initial gut microbiota from newborn infants to children reveals that diet determines its compositional development. *Journal of Microbiology and Biotechnology* 30 (7):1067–71. doi: 10.4014/jmb.2002.02042.

Kurilshikov, A., I. C. L. Van Den Munckhof, L. Chen, M. J. Bonder, K. Schraa, J. H. W. Rutten, N. P. Riksen, J. De Graaf, M. Oosting, S. Sanna, et al. 2019. Gut microbial associations to plasma metabolites linked to cardiovascular phenotypes and risk. *Circulation Research* 124 (12):1808–20. doi: 10.1161/CIRCRESAHA.118.314642.

La Rosa, P. S., B. B. Warner, Y. Zhou, G. M. Weinstock, E. Sodergren, C. M. Hall-Moore, H. J. Stevens, W. E. Bennett, Jr., N. Shaikh, L. A. Linneman, et al. 2014. Patterned progression of bacterial populations in the premature infant gut. *Proceedings of the National Academy of Sciences of the United States of America* 111 (34):12522–7. doi: 10.1073/pnas.1409497111.

Lach, G., H. Schellekens, T. G. Dinan, and J. F. Cryan. 2018. Anxiety, depression, and the microbiome: A role for gut peptides. *Neurotherapeutics* 15 (1):36–59. doi: 10.1007/s13311-017-0585-0.

Lagier, J. C., M. Million, P. Hugon, F. Armougom, and D. Raoult. 2012. Human gut microbiota: Repertoire and variations. *Frontiers in Cellular and Infection Microbiology* 2:136. doi: 10.3389/fcimb.2012.00136.

Lahtinen, S. J., L. Tammela, J. Korpela, R. Parhiala, H. Ahokoski, H. Mykkanen, and S. J. Salminen. 2009. Probiotics modulate the Bifidobacterium microbiota of elderly nursing home residents. *Age (Dordrecht, Netherlands)* 31 (1):59–66. doi: 10.1007/s11357-008-9081-0.

Lalles, J. P., P. Bosi, H. Smidt, and C. R. Stokes. 2007. Weaning - A challenge to gut physiologists. *Livestock Science* 108 (1–3):82–93. doi: 10.1016/j.livsci.2007.01.091.

Langille, M. G., C. J. Meehan, J. E. Koenig, A. S. Dhanani, R. A. Rose, S. E. Howlett, and R. G. Beiko. 2014. Microbial shifts in the aging mouse gut. *Microbiome* 2 (1):50. doi: 10.1186/s40168-014-0050-9.

Laursen, M. F., L. B. B. Andersen, K. F. Michaelsen, C. Molgaard, E. Trolle, M. I. Bahl, and T. R. Licht. 2016. Infant Gut microbiota development is driven by transition to family foods independent of maternal obesity. *Msphere* 1 (1):e00069-15. doi: 10.1128/mSphere.00069-15.

Levkovich, T., T. Poutahidis, C. Smillie, B. J. Varian, Y. M. Ibrahim, J. R. Lakritz, E. J. Alm, and S. E. Erdman. 2013. Probiotic bacteria induce a 'glow of health'. *PLoS One* 8 (1):e53867. doi: 10.1371/journal.pone.0053867.

Li, G. L., C. Xie, S. Y. Lu, R. G. Nichols, Y. Tian, L. C. Li, D. Patel, Y. Y. Ma, C. N. Brocker, T. T. Yan, et al. 2017. Intermittent fasting promotes white adipose browning and decreases obesity by shaping the gut microbiota. *Cell Metabolism* 26 (4):672–85.e4. doi: 10.1016/j.cmet.2017.08.019.

Li, J. Y., B. Chassaing, A. M. Tyagi, C. Vaccaro, T. Luo, J. Adams, T. M. Darby, M. N. Weitzmann, J. G. Mulle, A. T. Gewirtz, et al. 2016. Sex steroid deficiency-associated bone loss is microbiota dependent and prevented by probiotics. *The Journal of Clinical Investigation* 126 (6):2049–63. doi: 10.1172/JCI86062.

Li, K., L. Zhang, J. Xue, X. Yang, X. Dong, L. Sha, H. Lei, X. Zhang, L. Zhu, Z. Wang, et al. 2019. Dietary inulin alleviates diverse stages of type 2 diabetes mellitus via anti-inflammation and modulating gut microbiota in db/db mice. *Food & Function* 10 (4):1915–27. doi: 10.1039/c8fo02265h.

Liang, Q. Y., J. Chiu, Y. X. Chen, Y. Q. Huang, A. Higashimori, J. Y. Fang, H. Brim, H. Ashktorab, S. C. Ng, S. S. M. Ng, et al. 2017. Fecal bacteria act as novel biomarkers for noninvasive diagnosis of colorectal cancer. *Clinical Cancer Research* 23 (8):2061–70. doi: 10.1158/1078-0432.CCR-16-1599.

Lin, A., W. Zheng, Y. He, W. Tang, X. Wei, R. He, W. Huang, Y. Su, Y. Huang, H. Zhou, et al. 2018. Gut microbiota in patients with Parkinson's disease in southern China. *Parkinsonism & Related Disorders* 53:82–8. doi: 10.1016/j.parkreldis.2018.05.007.

Linden, D. R. 2014. Hydrogen sulfide signaling in the gastrointestinal tract. *Antioxidants & Redox Signaling* 20 (5):818–30. doi: 10.1089/ars.2013.5312.

Liu, H., X. Chen, X. Hu, H. Niu, R. Tian, H. Wang, H. Pang, L. Jiang, B. Qiu, Y. Zhang, et al. 2019. Alterations in the gut microbiome and metabolism with coronary artery disease severity. *Microbiome* 7 (1):68. doi: 10.1186/s40168-019-0683-9.

Liu, J., F. Wang, S. Liu, J. Du, X. Hu, J. Xiong, R. Fang, W. Chen, and J. Sun. 2017. Sodium butyrate exerts protective effect against Parkinson's disease in mice via stimulation of glucagon like peptide-1. *Journal of the Neurological Sciences* 381:176–81. doi: 10.1016/j.jns.2017.08.3235.

Liu, Y., S. Qin, Y. Song, Y. Feng, N. Lv, Y. Xue, F. Liu, S. Wang, B. Zhu, J. Ma, et al. 2019. The perturbation of infant gut microbiota caused by cesarean delivery is partially restored by exclusive breastfeeding. *Frontiers in Microbiology* 10:598. doi: 10.3389/fmicb.2019.00598.

Liu, Z., X. Dai, H. Zhang, R. Shi, Y. Hui, X. Jin, W. Zhang, L. Wang, Q. Wang, D. Wang, et al. 2020. Gut microbiota mediates intermittent-fasting alleviation of diabetes-induced cognitive impairment. *Nature Communications* 11 (1):855. doi: 10.1038/s41467-020-14676-4.

Long, X., C. C. Wong, L. Tong, E. S. H. Chu, C. Ho Szeto, M. Y. Y. Go, O. O. Coker, A. W. H. Chan, F. K. L. Chan, J. J. Y. Sung, et al. 2019. Peptostreptococcus anaerobius promotes colorectal carcinogenesis and modulates tumour immunity. *Nature Microbiology* 4 (12):2319–30. doi: 10.1038/s41564-019-0541-3.

Luan, Z., G. Sun, Y. Huang, Y. Yang, R. Yang, C. Li, T. Wang, D. Tan, S. Qi, C. Jun, et al. 2020. Metagenomics study reveals changes in gut microbiota in centenarians: A cohort study of Hainan centenarians. *Frontiers in Microbiology* 11:1474. doi: 10.3389/fmicb.2020.01474.

Luo, Y., E. N. Tixier, and A. M. Grinspan. 2020. Fecal microbiota transplantation for clostridioides difficile in high-risk older adults is associated with early recurrence. *Digestive Diseases and Sciences* 65 (12):3647–51. doi: 10.1007/s10620-020-06147-z.

Magne, F., W. Hachelaf, A. Suau, G. Boudraa, I. Mangin, M. Touhami, K. Bouziane-Nedjadi, and P. Pochart. 2006. A longitudinal study of infant faecal microbiota during weaning. *FEMS Microbiology Ecology* 58 (3):563–71. doi: 10.1111/j.1574-6941.2006.00182.x.

Magne, F., A. Puchi Silva, B. Carvajal, and M. Gotteland. 2017. The elevated rate of cesarean section and its contribution to non-communicable chronic diseases in Latin America: The growing involvement of the microbiota. *Frontiers in Pediatrics* 5:192. doi: 10.3389/fped.2017.00192.

Mahmoudiandehkordi, S., M. Arnold, K. Nho, S. Ahmad, W. Jia, G. Xie, G. Louie, A. Kueider-Paisley, M. A. Moseley, J. W. Thompson, et al. 2019. Altered bile acid profile associates with cognitive impairment in Alzheimer's disease-An emerging role for gut microbiome. *Alzheimer's & Dementia*15 (1):76–92. doi: 10.1016/j.jalz.2018.07.217.

Maini Rekdal, V., E. N. Bess, J. E. Bisanz, P. J. Turnbaugh, and E. P. Balskus. 2019. Discovery and inhibition of an interspecies gut bacterial pathway for Levodopa metabolism. *Science* 364 (6445):eaau6323. doi: 10.1126/science.aau6323.

Mantzorou, M., K. Vadikolias, E. Pavlidou, C. Tryfonos, G. Vasios, A. Serdari, and C. Giaginis. 2020. Mediterranean diet adherence is associated with better cognitive status and less depressive symptoms in a Greek elderly population. *Aging Clinical and Experimental Research*. doi: 10.1007/s40520-020-01608-x.

Mariat, D., O. Firmesse, F. Levenez, V. Guimarăes, H. Sokol, J. Doré, G. Corthier, and J.-P. Furet. 2009. The Firmicutes/Bacteroidetes ratio of the human microbiota changes with age. *BMC Microbiology* 9:123. doi: 10.1186/1471-2180-9-123.

Mateos, I., S. Combes, G. Pascal, L. Cauquil, C. Barilly, A. M. Cossalter, J. Laffitte, S. Botti, P. Pinton, and I. P. Oswald. 2018. Fumonisin-exposure impairs age-related ecological succession of bacterial species in weaned pig gut microbiota. *Toxins (Basel)* 10 (6):230. doi: 10.3390/toxins10060230.

Mima, K., R. Nishihara, Z. R. Qian, Y. Cao, Y. Sukawa, J. A. Nowak, J. Yang, R. Dou, Y. Masugi, M. Song, et al. 2016. Fusobacterium nucleatum in colorectal carcinoma tissue and patient prognosis. *Gut* 65 (12):1973–80. doi: 10.1136/gutjnl-2015-310101.

Miyazaki, K., N. Masuoka, M. Kano, and R. Iizuka. 2014. Bifidobacterium fermented milk and galacto-oligosaccharides lead to improved skin health by decreasing phenols production by gut microbiota. *Beneficial Microbes* 5 (2):121–8. doi: 10.3920/Bm2012.0066.

Moreno, I., I. Garcia-Grau, D. Bau, D. Perez-Villaroya, M. Gonzalez-Monfort, F. Vilella, R. Romero, and C. Simon. 2020. The first glimpse of the endometrial microbiota in early pregnancy. *American Journal of Obstetrics and Gynecology* 222 (4):296–305. doi: 10.1016/j.ajog.2020.01.031.

Morrison, K. E., E. Jasarevic, C. D. Howard, and T. L. Bale. 2020. It's the fiber, not the fat: Significant effects of dietary challenge on the gut microbiome. *Microbiome* 8 (1):15. doi: 10.1186/s40168-020-0791-6.

Mulders, R. J., K. C. G. De Git, E. Schele, S. L. Dickson, Y. Sanz, and R. a H. Adan. 2018. Microbiota in obesity: Interactions with enteroendocrine, immune and central nervous systems. *Obesity Reviews*19 (4):435–51. doi: 10.1111/obr.12661.

Nam, B., S. A. Kim, S. D. Park, H. J. Kim, J. S. Kim, C. H. Bae, J. Y. Kim, W. Nam, J. L. Lee, and J. H. Sim. 2020. Regulatory effects of Lactobacillus plantarum HY7714 on skin health by improving intestinal condition. *PLoS One* 15 (4):e0231268. doi: 10.1371/journal.pone.0231268.

Nay, K., M. Jollet, B. Goustard, N. Baati, B. Vernus, M. Pontones, L. Lefeuvre-Orfila, C. Bendavid, O. Rue, M. Mariadassou, et al. 2019. Gut bacteria are critical for optimal muscle function: A potential link with glucose homeostasis. *American Journal of Physiology. Endocrinology and Metabolism* 317 (1):E158–E171. doi: 10.1152/ajpendo.00521.2018.

Newgard, C. B. 2012. Interplay between lipids and branched-chain amino acids in development of insulin resistance. *Cell Metabolism* 15 (5):606–14. doi: 10.1016/j.cmet.2012.01.024.

Neyrinck, A. M., B. Taminiau, H. Walgrave, G. Daube, P. D. Cani, L. B. Bindels, and N. M. Delzenne. 2017. Spirulina protects against hepatic inflammation in aging: An effect related to the modulation of the gut microbiota? *Nutrients* 9 (6):633. doi: 10.3390/nu9060633.

Ni Lochlainn, M., R. C. E. Bowyer, and C. J. Steves. 2018. Dietary protein and muscle in aging people: The potential role of the gut microbiome. *Nutrients* 10 (7):929. doi: 10.3390/nu10070929.

Ni, Y. H., X. Yang, L. J. Zheng, Z. Wang, L. X. Wu, J. L. Jiang, T. Q. Yang, L. Y. Ma, and Z. W. Fu. 2019. Lactobacillus and Bifidobacterium improves physiological function and cognitive ability in aged mice by the regulation of gut microbiota. *Molecular Nutrition & Food Research* 63 (22):1900603. doi: 10.1002/mnfr.201900603.

Novince, C. M., C. R. Whittow, J. D. Aartun, J. D. Hathaway, N. Poulides, M. B. Chavez, H. M. Steinkamp, K. A. Kirkwood, E. Huang, C. Westwater, et al. 2017. Commensal gut microbiota immunomodulatory actions in bone marrow and liver have catabolic effects on skeletal homeostasis in health. *Scientific Reports* 7 (1):5747. doi: 10.1038/S41598-017-06126-X.

Nuli, R., J. Azhati, J. Cai, A. Kadeer, B. Zhang, and P. Mohemaiti. 2019. Metagenomics and faecal metabolomics integrative analysis towards the impaired glucose regulation and type 2 diabetes in uyghur-related omics. *Journal of Diabetes Research* 2019:2893041. doi: 10.1155/2019/2893041.

O'hara, A. M., and F. Shanahan. 2006. The gut flora as a forgotten organ. *EMBO Reports* 7 (7):688–93. doi: 10.1038/sj.embor.7400731.

O'neill, C. A., G. Monteleone, J. T. Mclaughlin, and R. Paus. 2016. The gut-skin axis in health and disease: A paradigm with therapeutic implications. *BioEssays* 38 (11):1167–76. doi: 10.1002/bies.201600008.

O'toole, P. W., and I. B. Jeffery. 2015. Gut microbiota and aging. *Science (New York, N.Y.)* 350 (6265):1214–5. doi: 10.1126/science.aac8469.

Ogawa, M., A. Saiki, Y. Matsui, N. Tsuchimoto, Y. Nakakita, Y. Takata, and T. Nakamura. 2016. Effects of oral intake of heat-killed Lactobacillus brevis SBC8803 (SBL88) on dry skin conditions: A randomized, double-blind, placebo-controlled study. *Experimental and Therapeutic Medicine* 12 (6):3863–72. doi: 10.3892/etm.2016.3862.

Ohlsson, C., C. Engdahl, F. Fak, A. Andersson, S. H. Windahl, H. H. Farman, S. Moverare-Skrtic, U. Islander, and K. Sjogren. 2014. Probiotics protect mice from ovariectomy-induced cortical bone loss. *PLoS One* 9 (3):e92368. doi: 10.1371/journal.pone.0092368.

Oishi, Y., and I. Manabe. 2016. Macrophages in age-related chronic inflammatory diseases. *NPJ Aging and Mechanisms of Disease* 2: 16018. doi: 10.1038/npjamd.2016.18.

Olszak, T., D. D. An, S. Zeissig, M. P. Vera, J. Richter, A. Franke, J. N. Glickman, R. Siebert, R. M. Baron, D. L. Kasper, et al. 2012. Microbial exposure during early life has persistent effects on natural killer T cell function. *Science (New York, N.Y.)* 336 (6080):489–93. doi: 10.1126/science.1219328.

Olveira, G., and I. Gonzalez-Molero. 2016. An update on probiotics, prebiotics and symbiotics in clinical nutrition. *Endocrinologia y Nutricion*63 (9):482–94. doi: 10.1016/j.endonu.2016.07.006.

Pan, F., L. Zhang, M. Li, Y. Hu, B. Zeng, H. Yuan, L. Zhao, and C. Zhang. 2018. Predominant gut Lactobacillus murinus strain mediates anti-inflammaging effects in calorie-restricted mice. *Microbiome* 6 (1):54. doi: 10.1186/s40168-018-0440-5.

Park, M. R., S. Ryu, B. E. Maburutse, N. S. Oh, S. H. Kim, S. Oh, S.-Y. Jeong, D.-Y. Jeong, S. Oh, and Y. Kim. 2018. Probiotic Lactobacillus fermentum strain JDFM216 stimulates the longevity and immune response of Caenorhabditis elegans through a nuclear hormone receptor. *Scientific Reports* 8 (1):7441. doi: 10.1038/s41598-018-25333-8.

Passarino, G., F. De Rango, and A. Montesanto. 2016. Human longevity: Genetics or lifestyle? It takes two to tango. *Immunity & Ageing: I & A* 13:12. doi: 10.1186/s12979-016-0066-z.

Petersen, N., F. Reimann, S. Bartfeld, H. F. Farin, F. C. Ringnalda, R. G. Vries, S. Van Den Brink, H. Clevers, F. M. Gribble, and E. J. De Koning. 2014. Generation of L cells in mouse and human small intestine organoids. *Diabetes* 63 (2):410–20. doi: 10.2337/db13-0991.

Petrov, V. A., I. V. Saltykova, I. A. Zhukova, V. M. Alifirova, N. G. Zhukova, Y. B. Dorofeeva, A. V. Tyakht, B. A. Kovarsky, D. G. Alekseev, E. S. Kostryukova, et al. 2017. Analysis of gut microbiota in patients with Parkinson's disease. *Bulletin of Experimental Biology and Medicine* 162 (6):734–7. doi: 10.1007/s10517-017-3700-7.

Pham, L., B. Kaiser, A. Romsa, T. Schwarz, R. Gopalakrishnan, E. D. Jensen, and K. C. Mansky. 2011. HDAC3 and HDAC7 have opposite effects on osteoclast differentiation. *The Journal of Biological Chemistry* 286 (14):12056–65. doi: 10.1074/jbc.M110.216853.

Picca, A., F. Fanelli, R. Calvani, G. Mule, V. Pesce, A. Sisto, C. Pantanelli, R. Bernabei, F. Landi, and E. Marzetti. 2018. Gut dysbiosis and muscle aging: Searching for novel targets against Sarcopenia. *Mediators of Inflammation* 2018:7026198. doi: 10.1155/2018/7026198.

Pipan, M. Z., L. Kajdic, A. Kalin, T. Plavec, and I. Zdovc. 2020. Do newborn puppies have their own microbiota at birth? Influence of type of birth on newborn puppy microbiota. *Theriogenology* 152: 18–28. doi: 10.1016/j.theriogenology.2020.04.014.

Prioult, G., and C. Nagler-Anderson. 2005. Mucosal immunity and allergic responses: Lack of regulation and/or lack of microbial stimulation? *Immunological Reviews* 206:204–18. doi: 10.1111/j.0105-2896.2005.00277.x.

Puertollano, E., S. Kolida, and P. Yaqoob. 2014. Biological significance of short-chain fatty acid metabolism by the intestinal microbiome. *Current Opinion in Clinical Nutrition and Metabolic Care* 17 (2): 139–44. doi: 10.1097/Mco.0000000000000025.

Qian, Y. W., X. D. Yang, S. Q. Xu, C. Y. Wu, Y. Y. Song, N. Qin, S. D. Chen, and Q. Xiao. 2018. Alteration of the fecal microbiota in Chinese patients with Parkinson's disease. *Brain, Behavior, and Immunity* 70:194–202. doi: 10.1016/j.bbi.2018.02.016.

Qin, J., Y. Li, Z. Cai, S. Li, J. Zhu, F. Zhang, S. Liang, W. Zhang, Y. Guan, D. Shen, et al. 2012. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 490 (7418):55–60. doi: 10.1038/nature11450.

Rajilic-Stojanovic, M., H. G. Heilig, D. Molenaar, K. Kajander, A. Surakka, H. Smidt, and W. M. De Vos. 2009. Development and application of the human intestinal tract chip, a phylogenetic microarray: Analysis of universally conserved phylotypes in the abundant microbiota of young and elderly adults. *Environmental Microbiology* 11 (7):1736–51. doi: 10.1111/j.1462-2920.2009.01900.x.

Rampelli, S., M. Candela, S. Turroni, E. Biagi, S. Collino, C. Franceschi, P. W. O'toole, and P. Brigidi. 2013. Functional metagenomic profiling of intestinal microbiome in extreme ageing. *Aging* 5 (12):902–12. doi: 10.18632/aging.100623.

Rampelli, S., M. Soverini, F. D'Amico, M. Barone, T. Tavella, D. Monti, M. Capri, A. Astolfi, P. Brigidi, E. Biagi, et al. 2020. Shotgun metagenomics of gut microbiota in humans with up to extreme longevity and the increasing role of xenobiotic degradation. *mSystems* 5 (2):00124-20. doi: 10.1128/mSystems.00124-20.

Reddel, S., F. Del Chierico, A. Quagliariello, S. Giancristoforo, P. Vernocchi, A. Russo, A. Fiocchi, P. Rossi, L. Putignani, and M. El Hachem. 2019. Gut microbiota profile in children affected by atopic dermatitis and evaluation of intestinal persistence of a probiotic mixture. *Scientific Reports* 9 (1):4996. doi: 10.1038/s41598-019-41149-6.

Reigadas, E., L. Alcala, M. Marin, A. Martin, and E. Bouza. 2017. Clinical, immunological and microbiological predictors of poor outcome in Clostridium difficile infection. *Diagnostic Microbiology and Infectious Disease* 88 (4):330–4. doi: 10.1016/j.diagmicrobio.2017.05.005.

Rogier, E. W., A. L. Frantz, M. E. Bruno, L. Wedlund, D. A. Cohen, A. J. Stromberg, and C. S. Kaetzel. 2014. Secretory antibodies in breast milk promote long-term intestinal homeostasis by regulating the gut microbiota and host gene expression. *Proceedings of the National Academy of Sciences of the United States of America* 111 (8):3074–9. doi: 10.1073/pnas.1315792111.

Rosier, B. T., P. D. Marsh, and A. Mira. 2018. Resilience of the oral microbiota in health: mechanisms that prevent dysbiosis. *Journal of Dental Research* 97 (4):371–80. doi: 10.1177/0022034517742139.

Rutayisire, E., K. Huang, Y. Liu, and F. Tao. 2016. The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: A systematic review. *BMC Gastroenterology* 16 (1):86. doi: 10.1186/s12876-016-0498-0.

Safari, Z., and P. Gerard. 2019. The links between the gut microbiome and non-alcoholic fatty liver disease (NAFLD). *Cellular and Molecular Life Sciences: CMLS* 76 (8):1541–58. doi: 10.1007/s00018-019-03011-w.

Saint-Georges-Chaumet, Y., and M. Edeas. 2016. Microbiota-mitochondria inter-talk: Consequence for microbiota-host interaction. *Pathogens and Disease* 74 (1):ftv096. doi: 10.1093/femspd/ftv096.

Salem, I., A. Ramser, N. Isham, and M. A. Ghannoum. 2018. The gut microbiome as a major regulator of the gut-skin axis. *Frontiers in Microbiology* 9:1459. doi: 10.3389/Fmicb.2018.01459.

Sampson, T. R., J. W. Debelius, T. Thron, S. Janssen, G. G. Shastri, Z. E. Ilhan, C. Challis, C. E. Schretter, S. Rocha, V. Gradinaru, et al. 2016. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell* 167 (6):1469–80.e12. doi: 10.1016/j.cell.2016.11.018.

Savignac, H. M., M. Tramullas, B. Kiely, T. G. Dinan, and J. F. Cryan. 2015. Bifidobacteria modulate cognitive processes in an anxious mouse strain. *Behavioural Brain Research* 287(:59–72. doi: 10.1016/j.bbr.2015.02.044.

Schwarz, A., A. Bruhs, and T. Schwarz. 2017. The short-chain fatty acid sodium butyrate functions as a regulator of the skin immune

system. *The Journal of Investigative Dermatology* 137 (4):855–64. doi: 10.1016/j.jid.2016.11.014.

Schwiertz, A., G. Le Blay, and M. Blaut. 2000. Quantification of different Eubacterium spp. in human fecal samples with species-specific 16S rRNA-targeted oligonucleotide probes. *Applied and Environmental Microbiology* 66 (1):375–82. doi: 10.1128/aem.66.1.375-382.2000.

Selma-Royo, M., I. Garcia-Mantrana, M. Calatayud, A. Parra-Llorca, C. Martinez-Costa, and M. C. Collado. 2020. Maternal diet during pregnancy and intestinal markers are associated with early gut microbiota. *European Journal of Nutrition*. doi: 10.1007/s00394-020-02337-7.

Serreli, G., and M. Deiana. 2020. Extra virgin olive oil polyphenols: Modulation of cellular pathways related to oxidant species and inflammation in aging. *Cells* 9 (2):478. doi: 10.3390/cells9020478.

Shannon, O. M., B. C. M. Stephan, A. Granic, M. Lentjes, S. Hayat, A. Mulligan, C. Brayne, K. T. Khaw, R. Bundy, S. Aldred, et al. 2019. Mediterranean diet adherence and cognitive function in older UK adults: The European Prospective Investigation into Cancer and Nutrition-Norfolk (EPIC-Norfolk) Study. *The American Journal of Clinical Nutrition* 110 (4):938–48. doi: 10.1093/ajcn/nqz114.

Shapiro, H., C. A. Thaiss, M. Levy, and E. Elinav. 2014. The cross talk between microbiota and the immune system: Metabolites take center stage. *Current Opinion in Immunology* 30:54–62. doi: 10.1016/j.coi.2014.07.003.

Sharma, K., M. Pooranachithra, K. Balamurugan, and G. Goel. 2019. Multivariate analysis of increase in life span of caenorhabditis elegans through intestinal colonization by indigenous probiotic strains. *Probiotics and Antimicrobial Proteins* 11 (3):865–73. doi: 10.1007/s12602-018-9420-0.

Sharma, M., and G. Shukla. 2020. Administration of metabiotics extracted from probiotic Lactobacillus rhamnosus MD 14 inhibit experimental colorectal carcinogenesis by targeting Wnt/β-catenin pathway. *Frontiers in Oncology* 10:746. doi: 10.3389/fonc.2020.00746.

Sharma, R., R. Kapila, G. Dass, and S. Kapila. 2014. Improvement in Th1/Th2 immune homeostasis, antioxidative status and resistance to pathogenic E. coli on consumption of probiotic Lactobacillus rhamnosus fermented milk in aging mice. *Age (Dordrecht, Netherlands)* 36 (4):9686. doi: 10.1007/s11357-014-9686-4.

Sharma, S., A. L. Dominguez, and J. Lustgarten. 2006. High accumulation of T regulatory cells prevents the activation of immune responses in aged animals. *Journal of Immunology (Baltimore, Md.: 1950)* 177 (12):8348–55. doi: 10.4049/jimmunol.177.12.8348.

Shi, Y. C., H. Guo, J. Chen, G. Sun, R. R. Ren, M. Z. Guo, L. H. Peng, and Y. S. Yang. 2018. Initial meconium microbiome in Chinese neonates delivered naturally or by cesarean section. *Scientific Reports* 8 (1):3255. doi: 10.1038/s41598-018-21657-7.

Shin, J. H., Y. N. Gao, J. H. Moore, D. T. Bolick, G. L. Kolling, M. Wu, and C. A. Warren. 2018. Innate immune response and outcome of clostridium difficile infection are dependent on fecal bacterial composition in the aged host. *The Journal of Infectious Diseases* 217 (2):188–97. doi: 10.1093/infdis/jix414.

Singh, H., M. G. Torralba, K. J. Moncera, L. Dilello, J. Petrini, K. E. Nelson, and R. Pieper. 2019. Gastro-intestinal and oral microbiome signatures associated with healthy aging. *Geroscience* 41 (6):907–21. doi: 10.1007/s11357-019-00098-8.

Smith, B. J., R. A. Miller, A. C. Ericsson, D. C. Harrison, R. Strong, and T. M. Schmidt. 2019. Changes in the gut microbiome and fermentation products concurrent with enhanced longevity in acarbose-treated mice. *BMC Microbiology* 19 (1):130. doi: 10.1186/s12866-019-1494-7.

Smith, P., D. Willemsen, M. Popkes, F. Metge, E. Gandiwa, M. Reichard, and D. R. Valenzano. 2017. Regulation of life span by the gut microbiota in the short-lived African turquoise killifish. *eLife* 6:e27014. doi: 10.7554/eLife.27014.

Sommer, F., J. M. Anderson, R. Bharti, J. Raes, and P. Rosenstiel. 2017. The resilience of the intestinal microbiota influences health and disease. *Nature Reviews. Microbiology* 15 (10):630–8. doi: 10.1038/nrmicro.2017.58.

Sorgdrager, F. J. H., P. J. W. Naude, I. P. Kema, E. A. Nollen, and P. P. Deyn. 2019. Tryptophan metabolism in inflammaging: From biomarker to therapeutic target. *Frontiers in Immunology* 10:2565. doi: 10.3389/fimmu.2019.02565.

Soto, M., C. Herzog, J. A. Pacheco, S. Fujisaka, K. Bullock, C. B. Clish, and C. R. Kahn. 2018. Gut microbiota modulate neurobehavior through changes in brain insulin sensitivity and metabolism. *Molecular Psychiatry* 23 (12):2287–301. doi: 10.1038/s41380-018-0086-5.

Soysal, P., A. T. Isik, A. F. Carvalho, B. S. Fernandes, M. Solmi, P. Schofield, N. Veronese, and B. Stubbs. 2017. Oxidative stress and frailty: A systematic review and synthesis of the best evidence. *Maturitas* 99:66–72. doi: 10.1016/j.maturitas.2017.01.006.

Stinson, L. F., M. C. Boyce, M. S. Payne, and J. A. Keelan. 2019. The not-so-sterile womb: Evidence that the human fetus is exposed to bacteria prior to birth. *Frontiers in Microbiology* 10:1124. doi: 10.3389/Fmicb.2019.01124.

Subramanian, S., S. Huq, T. Yatsunenko, R. Haque, M. Mahfuz, M. A. Alam, A. Benezra, J. Destefano, M. F. Meier, B. D. Muegge, et al. 2014. Persistent gut microbiota immaturity in malnourished Bangladeshi children. *Nature* 510 (7505):417–21. doi: 10.1038/nature13421.

Sugawara, T., and K. Sakamoto. 2018. Killed Bifidobacterium longum enhanced stress tolerance and prolonged life span of Caenorhabditis elegans via DAF-16. *The British Journal of Nutrition* 120 (8):872–80. doi: 10.1017/S0007114518001563.

Sun, J., S. Liu, Z. Ling, F. Wang, Y. Ling, T. Gong, N. Fang, S. Ye, J. Si, and J. Liu. 2019. Fructooligosaccharides ameliorating cognitive deficits and neurodegeneration in APP/PS1 transgenic mice through modulating gut microbiota. *Journal of Agricultural and Food Chemistry* 67 (10):3006–17. doi: 10.1021/acs.jafc.8b07313.

Sun, J., J. Xu, Y. Ling, F. Wang, T. Gong, C. Yang, S. Ye, K. Ye, D. Wei, Z. Song, et al. 2019. Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice. *Translational Psychiatry* 9 (1):189. doi: 10.1038/s41398-019-0525-3.

Sun, J., J. Xu, B. Yang, K. Chen, Y. Kong, N. Fang, T. Gong, F. Wang, Z. Ling, and J. Liu. 2020. Effect of Clostridium butyricum against microglia-mediated neuroinflammation in Alzheimer's disease via regulating gut microbiota and metabolites butyrate. *Molecular Nutrition & Food Research* 64 (2):e1900636. doi: 10.1002/mnfr.201900636.

Szanto, M., A. Dozsa, D. Antal, K. Szabo, L. Kemeny, and P. Bai. 2019. Targeting the gut-skin axis-Probiotics as new tools for skin disorder management? *Experimental Dermatology* 28 (11):1210–8. doi: 10.1111/exd.14016.

Tapiainen, T., N. Paalanne, M. V. Tejesvi, P. Koivusaari, K. Korpela, T. Pokka, J. Salo, T. Kaukola, A. M. Pirttila, M. Uhari, et al. 2018. Maternal influence on the fetal microbiome in a population-based study of the first-pass meconium. *Pediatric Research* 84 (3):371–9. doi: 10.1038/pr.2018.29.

Thevaranjan, N., A. Puchta, C. Schulz, A. Naidoo, J. C. Szamosi, C. P. Verschoor, D. Loukov, L. P. Schenck, J. Jury, K. P. Foley, et al. 2017. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. *Cell Host & Microbe* 21 (4):455–66 e454. doi: 10.1016/j.chom.2017.03.002.

Thevaranjan, N., A. Puchta, C. Schulz, A. Naidoo, J. C. Szamosi, C. P. Verschoor, D. Loukov, L. P. Schenck, J. Jury, K. P. Foley, et al. 2018. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. *Cell Host & Microbe* 23 (4):570. doi: 10.1016/j.chom.2018.03.006.

Ticinesi, A., A. Nouvenne, N. Cerundolo, P. Catania, B. Prati, C. Tana, and T. Meschi. 2019. Gut microbiota, muscle mass and function in aging: A focus on physical frailty and sarcopenia. *Nutrients* 11 (7):1633. doi: 10.3390/nu11071633.

Toya, T., M. T. Corban, E. Marrietta, I. E. Horwath, L. O. Lerman, J. A. Murray, and A. Lerman. 2020. Coronary artery disease is associated with an altered gut microbiome composition. *PLoS One* 15 (1):e0227147. doi: 10.1371/journal.pone.0227147.

Tuomisto, S., H. Huhtala, M. Martiskainen, S. Goebeler, T. Lehtimaki, and P. J. Karhunen. 2019. Age-dependent association of gut bacteria with coronary atherosclerosis: Tampere Sudden Death Study. *PLoS One* 14 (8):e0221345. doi: 10.1371/journal.pone.0221345.

Turnbaugh, P. J., R. E. Ley, M. A. Mahowald, V. Magrini, E. R. Mardis, and J. I. Gordon. 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444 (7122):1027–31. doi: 10.1038/nature05414.

Tyagi, A. M., M. Yu, T. M. Darby, C. Vaccaro, J. Y. Li, J. A. Owens, E. Hsu, J. Adams, M. N. Weitzmann, R. M. Jones, et al. 2018. The microbial metabolite butyrate stimulates bone formation via T regulatory cell-mediated regulation of WNT10B expression. *Immunity* 49 (6):1116–31 e1117. doi: 10.1016/j.immuni.2018.10.013.

Unger, M. M., J. Spiegel, K.-U. Dillmann, D. Grundmann, H. Philippeit, J. Bürmann, K. Faßbender, A. Schwiertz, and K.-H. Schäfer. 2016. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. *Parkinsonism & Related Disorders* 32:66–72. doi: 10.1016/j.parkreldis.2016.08.019.

Vael, C., S. L. Verhulst, V. Nelen, H. Goossens, and K. N. Desager. 2011. Intestinal microflora and body mass index during the first three years of life: An observational study. *Gut Pathogens* 3 (1):8. doi: 10.1186/1757-4749-3-8.

Valles, Y., A. Artacho, A. Pascual-Garcia, M. L. Ferrus, M. J. Gosalbes, J. J. Abellan, and M. P. Francino. 2014. Microbial succession in the gut: Directional trends of taxonomic and functional change in a birth cohort of Spanish infants. *PLoS Genetics* 10 (6):e1004406. doi: 10.1371/journal.pgen.1004406.

Van Kessel, S. P., A. K. Frye, A. O. El-Gendy, M. Castejon, A. Keshavarzian, G. Van Dijk, and S. El Aidy. 2019. Gut bacterial tyrosine decarboxylases restrict levels of levodopa in the treatment of Parkinson's disease. *Nature Communications* 10 (1):310. doi: 10.1038/s41467-019-08294-y.

Van Opstal, E., G. L. Kolling, J. H. Moore, II, C. M. Coquery, N. S. Wade, W. M. Loo, D. T. Bolick, J. H. Shin, L. D. Erickson, and C. A. Warren. 2016. Vancomycin treatment alters humoral immunity and intestinal microbiota in an aged mouse model of clostridium difficile infection. *The Journal of Infectious Diseases* 214 (1):130–9. doi: 10.1093/infdis/jiw071.

Van Tongeren, S. P., J. P. Slaets, H. J. Harmsen, and G. W. Welling. 2005. Fecal microbiota composition and frailty. *Applied and Environmental Microbiology* 71 (10):6438–42. doi: 10.1128/AEM.71.10.6438-6442.2005.

Vandenplas, Y., V. P. Carnielli, J. Ksiazyk, M. S. Luna, N. Migacheva, J. M. Mosselmans, J. C. Picaud, M. Possner, A. Singhal, and M. Wabitsch. 2020. Factors affecting early-life intestinal microbiota development. *Nutrition (Burbank, Los Angeles County, Calif.)* 78:110812. doi: 10.1016/j.nut.2020.110812.

Vemuri, R., R. Gundamaraju, M. D. Shastri, S. D. Shukla, K. Kalpurath, M. Ball, S. Tristram, E. M. Shankar, K. Ahuja, and R. Eri. 2018. Gut microbial changes, interactions, and their implications on human lifecycle: An ageing perspective. *BioMed Research International* 2018:4178607. doi: 10.1155/2018/4178607.

Vendrik, K. E. W., R. E. Ooijevaar, P. R. C. De Jong, J. D. Laman, B. W. Van Oosten, J. J. Van Hilten, Q. R. Ducarmon, J. J. Keller, E. J. Kuijper, and M. F. Contarino. 2020. Fecal microbiota transplantation in neurological disorders. *Frontiers in Cellular and Infection Microbiology* 10:98. doi: 10.3389/fcimb.2020.00098.

Vetizou, M., J. M. Pitt, R. Daillere, P. Lepage, N. Waldschmitt, C. Flament, S. Rusakiewicz, B. Routy, M. P. Roberti, C. P. Duong, et al. 2015. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science (New York, N.Y.)* 350 (6264):1079–84. doi: 10.1126/science.aad1329.

Vogt, N. M., R. L. Kerby, K. A. Dill-Mcfarland, S. J. Harding, A. P. Merluzzi, S. C. Johnson, C. M. Carlsson, S. Asthana, H. Zetterberg, K. Blennow, et al. 2017. Gut microbiome alterations in Alzheimer's disease. *Scientific Reports* 7 (1):13537. doi: 10.1038/s41598-017-13601-y.

Wang, X., G. Sun, T. Feng, J. Zhang, X. Huang, T. Wang, Z. Xie, X. Chu, J. Yang, H. Wang, et al. 2019. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. *Cell Research* 29 (10):787–803. doi: 10.1038/s41422-019-0216-x.

Wang, Y., E. K. Mortimer, K. G. H. Katundu, N. Kalanga, L. E. X. Leong, G. L. Gopalsamy, C. T. Christophersen, A. C. Richard, A. Shivasami, G. C. J. Abell, et al. 2019. The capacity of the fecal microbiota from Malawian infants to ferment resistant starch. *Frontiers in Microbiology* 10:1459. doi: 10.3389/fmicb.2019.01459.

Wang, Z., E. Klipfell, B. J. Bennett, R. Koeth, B. S. Levison, B. Dugar, A. E. Feldstein, E. B. Britt, X. Fu, Y. M. Chung, et al. 2011. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature* 472 (7341):57–63. doi: 10.1038/nature09922.

Wegh, C. A. M., S. Y. Geerlings, J. Knol, G. Roeselers, and C. Belzer. 2019. Postbiotics and their potential applications in early life nutrition and beyond. *Int J Mol Sci* 20 (19):4673. doi: 10.3390/ijms20194673.

Willcox, B. J., D. C. Willcox, H. Todoriki, A. Fujiyoshi, K. Yano, Q. He, J. D. Curb, and M. Suzuki. 2007. Caloric restriction, the traditional Okinawan diet, and healthy aging: The diet of the world's longest-lived people and its potential impact on morbidity and life span. *Annals of the New York Academy of Sciences* 1114:434–55. doi: 10.1196/annals.1396.037.

Wilson, D., T. Jackson, E. Sapey, and J. M. Lord. 2017. Frailty and sarcopenia: The potential role of an aged immune system. *Ageing Research Reviews* 36:1–10. doi: 10.1016/j.arr.2017.01.006.

Windey, K., V. De Preter, and K. Verbeke. 2012. Relevance of protein fermentation to gut health. *Molecular Nutrition & Food Research* 56 (1):184–96. doi: 10.1002/mnfr.201100542.

Wong, M. C. S., J. Huang, V. Lok, J. Wang, F. Fung, H. Ding, and Z. J. Zheng. 2020. Differences in incidence and mortality trends of colorectal cancer worldwide based on sex, age, and anatomic location. *Clinical Gastroenterology and Hepatology*. doi: 10.1016/j.cgh.2020.02.026.

Wu, G. D., J. Chen, C. Hoffmann, K. Bittinger, Y. Y. Chen, S. A. Keilbaugh, M. Bewtra, D. Knights, W. A. Walters, R. Knight, et al. 2011. Linking long-term dietary patterns with gut microbial enterotypes. *Science (New York, N.Y.)* 334 (6052):105–8. doi: 10.1126/science.1208344.

Wu, H., E. Esteve, V. Tremaroli, M. T. Khan, R. Caesar, L. Manneras-Holm, M. Stahlman, L. M. Olsson, M. Serino, M. Planas-Felix, et al. 2017. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. *Nature Medicine* 23 (7):850–8. doi: 10.1038/nm.4345.

Wu, X. R., S. Mukewar, R. P. Kiran, F. H. Remzi, J. Hammel, and B. Shen. 2013. Risk factors for peristomal pyoderma gangrenosum complicating inflammatory bowel disease. *Journal of Crohn's & Colitis* 7 (5):e171–e177. doi: 10.1016/j.crohns.2012.08.001.

Xie, C., and D. Halegoua-Demarzio. 2019. Role of probiotics in nonalcoholic fatty liver disease: Does gut microbiota matter? *Nutrients* 11 (11):2837. doi: 10.3390/nu11112837.

Xu, J., B. Lawley, G. Wong, A. Otal, L. Chen, T. J. Ying, X. Lin, W. W. Pang, F. Yap, Y. S. Chong, et al. 2020. Ethnic diversity in infant gut microbiota is apparent before the introduction of complementary diets. *Gut Microbes* 11 (5):1362–73. doi: 10.1080/19490976.2020.1756150.

Yan, J., J. W. Herzog, K. Tsang, C. A. Brennan, M. A. Bower, W. S. Garrett, B. R. Sartor, A. O. Aliprantis, and J. F. Charles. 2016. Gut microbiota induce IGF-1 and promote bone formation and growth. *Proceedings of the National Academy of Sciences of the United States of America* 113 (47):E7554–63. doi: 10.1073/pnas.1607235113.

Yang, B., S. Yan, Y. Chen, R. P. Ross, C. Stanton, J. Zhao, H. Zhang, and W. Chen. 2020. Diversity of gut microbiota and bifidobacterial community of Chinese subjects of different ages and from different regions. *Microorganisms* 8 (8):1108. doi: 10.3390/microorganisms8081108.

Yang, J., and J. Yu. 2018. The association of diet, gut microbiota and colorectal cancer: What we eat may imply what we get. *Protein & Cell* 9 (5):474–87. doi: 10.1007/s13238-018-0543-6.

Yassour, M., T. Vatanen, H. Siljander, A. M. Hamalainen, T. Harkonen, S. J. Ryhanen, E. A. Franzosa, H. Vlamakis, C. Huttenhower, D. Gevers, et al. 2016. Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability. *Science Translational Medicine* 8 (343): 343ra381. doi: 10.1126/scitranslmed.aad0917.

Yoshida, N., T. Emoto, T. Yamashita, H. Watanabe, T. Hayashi, T. Tabata, N. Hoshi, N. Hatano, G. Ozawa, N. Sasaki, et al. 2018. Bacteroides vulgatus and bacteroides dorei reduce gut microbial lipopolysaccharide production and inhibit atherosclerosis. *Circulation* 138 (22):2486–98. doi: 10.1161/CIRCULATIONAHA.118.033714.

Yu, E. W., L. Gao, P. Stastka, M. C. Cheney, J. Mahabamunuge, M. Torres Soto, C. B. Ford, J. A. Bryant, M. R. Henn, and E. L. Hohmann. 2020. Fecal microbiota transplantation for the improvement of metabolism in obesity: The FMT-TRIM double-blind placebo-controlled pilot trial. *PLoS Medicine* 17 (3):e1003051. doi: 10.1371/journal.pmed.1003051.

Yu, F., W. Han, G. Zhan, S. Li, X. Jiang, L. Wang, S. Xiang, B. Zhu, L. Yang, A. Luo, et al. 2019. Abnormal gut microbiota composition contributes to the development of type 2 diabetes mellitus in db/db mice. *Aging* 11 (22):10454–67. doi: 10.18632/aging.102469.

Yu, H., Z. Guo, S. Shen, and W. Shan. 2016. Effects of taurine on gut microbiota and metabolism in mice. *Amino Acids* 48 (7):1601–17. doi: 10.1007/s00726-016-2219-y.

Yu, J., Q. Feng, S. H. Wong, D. Zhang, Q. Y. Liang, Y. W. Qin, L. Q. Tang, H. Zhao, J. Stenvang, Y. L. Li, et al. 2017. Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer. *Gut* 66 (1):70–8. doi: 10.1136/gutjnl-2015-309800.

Zaiss, M. M., R. M. Jones, G. Schett, and R. Pacifici. 2019. The gut-bone axis: How bacterial metabolites bridge the distance. *The Journal of Clinical Investigation* 129 (8):3018–28. doi: 10.1172/Jci128521.

Zhai, W., Y. Huang, X. Zhang, W. Fei, Y. Chang, S. Cheng, Y. Zhou, J. Gao, X. Tang, X. Zhang, et al. 2018. Profile of the skin microbiota in a healthy Chinese population. *The Journal of Dermatology* 45 (11):1289–300. doi: 10.1111/1346-8138.14594.

Zhang, C., S. Li, L. Yang, P. Huang, W. Li, S. Wang, G. Zhao, M. Zhang, X. Pang, Z. Yan, et al. 2013. Structural modulation of gut microbiota in life-long calorie-restricted mice. *Nature Communications* 4:2163. doi: 10.1038/ncomms3163.

Zhao, J., F. Tian, S. Yan, Q. Zhai, H. Zhang, and W. Chen. 2018. Lactobacillus plantarum CCFM10 alleviating oxidative stress and restoring the gut microbiota in d-galactose-induced aging mice. *Food & Function* 9 (2):917–24. doi: 10.1039/c7fo01574g.

Zhao, L., X. Qiao, J. Zhu, X. Zhang, J. Jiang, Y. Hao, and F. Ren. 2011. Correlations of fecal bacterial communities with age and living region for the elderly living in Bama, Guangxi, China. *Journal of Microbiology (Seoul, Korea)* 49 (2):186–92. doi: 10.1007/s12275-011-0405-x.

Zheng, J., X. Xiao, Q. Zhang, L. Mao, M. Yu, and J. Xu. 2015. The placental microbiome varies in association with low birth weight in full-term neonates. *Nutrients* 7 (8):6924–37. doi: 10.3390/nu7085315.

Zhong, H., J. Penders, Z. Shi, H. Ren, K. Cai, C. Fang, Q. Ding, C. Thijs, E. E. Blaak, C. D. A. Stehouwer, et al. 2019. Impact of early events and lifestyle on the gut microbiota and metabolic phenotypes in young school-age children. *Microbiome* 7 (1):2. doi: 10.1186/s40168-018-0608-z.

Zhou, P., Y. Zhou, B. Liu, Z. Jin, X. Zhuang, W. Dai, Z. Yang, X. Feng, Q. Zhou, Y. Liu, et al. 2020. Perinatal antibiotic exposure affects the transmission between maternal and neonatal microbiota and is associated with early-onset sepsis. *Msphere* 5 (1):00984-19. doi: 10.1128/mSphere.00984-19.

Zhu, L., S. S. Baker, C. Gill, W. Liu, R. Alkhouri, R. D. Baker, and S. R. Gill. 2013. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: A connection between endogenous alcohol and NASH. *Hepatology (Baltimore, Md.)* 57 (2): 601–9. doi: 10.1002/hep.26093.

Zhuang, Z. Q., L. L. Shen, W. W. Li, X. Fu, F. Zeng, L. Gui, Y. Lu, M. Cai, C. Zhu, Y. L. Tan, et al. 2018. Gut microbiota is altered in patients with Alzheimer's disease. *Journal of Alzheimer's Disease: JAD* 63 (4):1337–46. doi: 10.3233/Jad-180176.