Dysbiosis, malnutrition and enhanced gut-lung axis contribute to age-related respiratory diseases

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DYSBIOSIS, MALNUTRITION AND ENHANCED GUT-LUNG AXIS CONTRIBUTE TO AGE-RELATED RESPIRATORY DISEASES

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HIGHLIGHTS

- Older people are often malnourished and susceptible to develop lung diseases.
- Ageing is associated with dysbiotic microbiota and alteration of the gut-lung axis.
- Nutrition is an accessible lever affecting microbiota and ageing of the lung.
- Gut and lung microbiota represent key players in the maintenance of healthy lungs.
- Gut and lung microbiota are potential targets against ageing-related lung disease.

ABSTRACT

Older people are at an increased risk of developing respiratory diseases such as chronic obstructive pulmonary diseases, asthma, idiopathic pulmonary fibrosis or lung infections. Susceptibility to these diseases is partly due to the intrinsic ageing process, characterized by genomic, cellular and metabolic hallmarks and immunosenescence, and is associated with changes in the intestinal microbiota. Importantly, in the lungs, ageing is also associated with a dysbiosis and loss of resilience of the resident microbiota and alterations of the gut-lung axis. Notably, as malnutrition is often observed in the elderly, nutrition is one of the most accessible modifiable factors affecting both senescence and microbiota. This article reviews the changes affecting the lung and its resident microbiota during ageing, as well as the interconnections between malnutrition, senescence, microbiota, gut-lung axis and respiratory health. As the communication along the gut-lung axis becomes more permissive with ageing, this review also explores the evidence that the gut and lung microbiota are key players in the maintenance of healthy lungs, and as such, are potential targets for nutrition-based preventive strategies against lung disease in elderly populations.

Keywords: Age-associated lung diseases, Microbiota, Nutrition, Gut-Lung axis, Ageing, Respiratory infections.

INTRODUCTION.

Population worldwide is getting older; more than 1 billion people are over 60 and this number will continue to increase in the future, especially in developing countries. Failing to ensure healthy ageing in these elderly populations would lead to multiple negative consequences (personal, economic and societal) and it is, therefore, essential to prepare societies to meet their specific needs. This has been made a priority of the World Health Organization (WHO), which has elaborated the plan for a Decade of Healthy Ageing 2020–2030.

Ageing reflects all the changes taking place over the course of life. Its process has a high inter-individual variability with respect to its rate and affected organs, and is characterized by a decrease in physical capacity, an increased vulnerability to environmental challenges, and a growing risk of disease and death. Physiologically, loss in muscle mass, decline in strength (Leong et al., 2015; Rantanen et al., 2003), and increased risk of fracture, are commonly associated with ageing. Impairments in sensory functions, increased frequency of infections, falls, pressure ulcers and deterioration in cognitive functions (Fernández-Garrido et al., 2014; Fried et al., 1991; Inouye et al., 2007), are negatively correlated with survival (Kane et al., 2012; Lordos et al., 2008). Particularly, the elderly population is at risk of developing lung infections. The prevalence of other pulmonary diseases, (*e.g.* tuberculosis, chronic obstructive pulmonary diseases, asthma), increases with age and contributes to morbidity and mortality in older individuals. At a cellular level, ageing is associated with immunosenescence (Lang et al., 2012) and with chronic low-level inflammation, known as inflamm-ageing (Ferrucci and Fabbri, 2018).

Malnutrition is defined by the European Society for Clinical Nutrition and Metabolism as “a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease” (Cederholm et al., 2017). Importantly, it is also one of the first signs of a degrading health condition in the elderly population. Undernourished old people are at increased risk of falls, long hospital stays, infections,

impaired respiratory function and death (Rasheed and Woods, 2013; Tappenden et al., 2013). Interestingly, an early study by Heymsfield *et al*. showed an association between malnutrition and the apparition of further pathologies, including bronchopneumonia (Heymsfield et al., 1979). Thus, because nutrition is one of the most accessible modifiable factors, it can be considered as a lever of action to promote healthy ageing in older people (Rodgers and Collins, 2020).

Many clinical issues observed in ageing individuals are associated with changes in the microbiota composition and functionality in the gut and other organs (Claesson et al., 2012, 2011; Jackson et al., 2016; Jeffery et al., 2016; O'Sullivan et al., 2011). Although there is a very high inter-individual variability, multiple studies have shown that the diversity of gut microbiota and genera such as *Bifidobacteria* and *Lactobacilli* are reduced in older individuals, whereas certain opportunists (*e.g. Clostridioides difficile*) are increased (Claesson et al., 2011; Milani et al., 2016; Rea et al., 2012). Moreover, specific microbial profiles have been identified as longevity signatures in centenarians (Biagi et al., 2017; Cătoi et al., 2020; Kong et al., 2016; Naito et al., 2019; Rampelli et al., 2020; Santoro et al., 2018; N. Wang et al., 2019; Wu et al., 2020). In the lungs, due to the invasiveness of the procedure, no study has been performed on lower respiratory tract microbiota and only a few studies have described the composition of the upper respiratory tract (URT) microbiota in the elderly (de Steenhuijsen Piters et al., 2016; J.-J. Lee et al., 2019; Stearns et al., 2015; Whelan et al., 2014). It is not fully understood how the microbiota impacts ageing processes, but it is likely that dysbiosis plays a central role in the progression of ageing-related disorders and that restoration of eubiosis would promote healthy ageing (Figure 1).

Here, we review the hallmarks of the ageing lung and interconnections between malnutrition, ageing, specifically cellular senescence, microbiota and lung health. The evidence of the gut-lung axis and its specificities in the elderly population prompt us to propose that both gut and lung microbiota are main players in the maintenance of healthy lungs and, therefore, are central targets for nutrition based preventive strategies in elderly populations.

1. AGEING IN THE LUNGS

1.1. The ageing lung and the most prevalent age-related pulmonary diseases

According to the European Respiratory Society (ERS), the status of lung function is considered a predictor of healthy ageing (Meiners et al., 2015). For instance, elder individuals with poor lung function are prone to develop cardiovascular disease, type 2 diabetes (T2D) and cognitive decline, when compared to those individuals with robust lung function (Bowdish, 2019; Hole et al., 1996; Lange et al., 1990; Weiss et al., 1995). Conversely, in older adults, a robust lung function correlates with a higher metabolic rate, which is a well-known parameter for fitness, activity and physical performance in the elderly (Bowdish, 2019; Choi and Pai, 2004; Simpson et al., 2005).

Although the ageing of the lung is inevitable, and leads to a natural decline in its function, there are intrinsic (*e.g.,* genetic components) and extrinsic (*e.g.,* environment) factors that may accelerate or slow down this process. There are ten hallmarks thought to contribute to physiological changes associated with ageing and particularly with the ageing lung (Figure 2) (López-Otín et al., 2013; Meiners et al., 2015). These include 1) genomic instability, 2) telomere attrition, 3) epigenetic alterations, 4) loss of proteotasis, 5) deregulated nutrient sensing, 6) mitochondrial dysfunction, 7) cellular senescence, 8) stem cell exhaustion, 9) altered intercellular communication and 10) dysregulation of extracellular matrix (ECM). These alterations can occur in conducting airway epithelial cells, alveolar epithelial cells as well as airway smooth muscle cells and resident immune cells, and result in both structural and physiological changes. For instance, the increased apoptosis of epithelial cells, together with abnormalities of the microtubular structure of the cilia of multiciliated cells, the altered mucins and antioxidants content of the epithelium lining fluid and the decreased respiratory muscle and diaphragm strength, lead to defects in the mucociliary clearance machinery and a decreased ability of the lungs to clear mucus and inhaled particles and pathogens (Cho and Stout-Delgado, 2020; Ho et al., 2001; Wansleeben et al., 2014). The size of alveoli is also increased in the aged lungs, due to changes in the ECM and this leads to decreased elastic

recoil and increased end expiratory lung volume (Cho and Stout-Delgado, 2020; Janssens et al., 1999). These physiological changes that occur in the ageing lung collectively lead to poor lung functional capacity and a decreased ability to maintain homeostasis.

As a consequence of the natural accumulation of age-related physiological changes in addition to exposure to toxic environmental factors, this organ becomes susceptible to chronic disorders such as *Chronic Obstructive Pulmonary Disease (COPD), Idiopathic Pulmonary Fibrosis (IPF), Lung cancer and asthma,* and infectious diseases like *Community Acquired Pneumonia (CAP).* In particular, the age-associated alterations of the immune system, called immunosenescence and discussed in the next section, are thought to be a key driver of asthma exacerbation in the elderly (Cho and Stout-Delgado, 2020; Z. Li et al., 2017; Metcalf et al., 2015; Shaw et al., 2011). Similarly, immunosenescence is thought to be the main culprit for predisposing the ageing lung to immunopathology in response to infectious stimuli (Chen et al., 2020; Cho and Stout-Delgado, 2020; Goldstein, 2012) and consequently, the ageing lung is more predisposed to secondary bacterial infections consecutive to viral pneumonia (Akgün et al., 2012; Castle et al., 2007; Chen et al., 2020; Cho and Stout-Delgado, 2020; Goldstein, 2012). According to the WHO-Europe, older adults are at a significant increased risk of severe disease from SARS-CoV-2 infection; over 95% of the reported fatalities occurred in those individuals over 60 years old and with comorbidities. Recent data indicate clear effects on the immune system, which may be worsen in older individuals (F. Wang et al., 2020).

1.2. Immunosenescence and its impact on age-related pulmonary diseases

Immunosenescence is defined as the age-associated decline in the immune system capacity to respond to infections and generate long-term immune memory (Cho and Stout-Delgado, 2020). As a consequence, older individuals are prone to infection, cancer, autoimmunity and chronic inflammation, and exhibit a poor vaccine response (Al-Alawi et al., 2014; Fulop et al., 2014; Murray and Chotirmall, 2015). Globally, immunosenescence has the following traits: poor capacity to respond to new antigens, accumulation of memory T cells in detriment of a

diminished naïve T cell repertoire, and chronic low-grade inflammation state known as inflamm-ageing (Aiello et al., 2019). Both innate and adaptive immunity are affected by immunosenescence.

Immunosenescence of *alveolar macrophages* causes a decrease in their total numbers and capacity to perform phagocytosis and clearance of foreign particles, provoking susceptibility to bacterial and viral infections causing CAP (Chen et al., 2020; Volkova et al., 2012; Wong et al., 2017). It also diminishes the capacity of these cells to produce pro-resolution mediators, such as resolvins (Arnardottir et al., 2014), antioxidant/detoxification factors in response to cigarette smoke in COPD disease (Suzuki et al., 2008), or to clear away apoptotic airway epithelial cells generated during COPD (Chen et al., 2020; Hodge et al., 2003). Immunosenescence of airway mucosal *Dendritic Cells* (DCs) is reflected by lower expression and function of Toll-like receptors (TLRs), decreased phagocytosis capacity, and diminished/delayed migration potential towards draining lymph nodes upon activation (Agrawal et al., 2007; Agrawal and Gupta, 2011; Volkova et al., 2012). In the context of viral pneumonia, the capacity of DCs to prime naïve T cells against influenza is deficient due to a delayed infiltration kinetics of DCs into the aged lungs, and a defect of DCs migration from the lung into the draining lymph nodes (Valkenburg et al., 2012; Zhao et al., 2011). DCs also display age-associated defects in their ability to prime $CD8^+$ T cell responses through MHC-I-dependent antigen presentation (Zacca et al., 2015), and inflammasome activation and production of IL-1β (Chen et al., 2020; Stout-Delgado et al., 2012). Immunosenescence of *neutrophils*, the most abundant innate immune leukocyte, provokes an unregulated production of superoxide, deficient phagocytosis (Chen et al., 2014; Cho and Stout-Delgado, 2020; Corberand et al., 1981) and deficient formation of neutrophil extracellular traps (NETs) that correlates with defective bacterial clearance (Brinkmann and Zychlinsky, 2007). Immunosenescence also impacts neutrophil migration to the lung in response to stimuli but these cells tend to accumulate and prolong their stay in this organ (Kahlich et al., 1975). Together, these age-related alterations in neutrophil functions can have devastating consequences, as best exemplified in the current SARS-CoV-2 pneumonia epidemic (Barnes

et al., 2020; Chen et al., 2020). Indeed, not only is the neutrophil accumulation well-documented across mouse and large animals during influenza infection, but COVID-19 patients who succumb, display a two-fold increase in neutrophilia, contributing to the age-enhanced mortality to SARS-CoV-2 infection (Barnes et al., 2020; Liu et al., 2020; D. Wang et al., 2020).

In the adaptive immune system, immunosenescence is best reflected in the *T cell compartment*, which increases the ratio of $CD4^+$ to $CD8^+$ T cells in the bronchoalveolar fluid, suggesting that the pool of lung resident memory $CD4^+$ T cells also augments as a function of age (Haynes and Swain, 2006; Kovaiou and Grubeck-Loebenstein, 2006). The systemic and local increases in memory T cells are thought to contribute to the T cell-driven asthma in the elderly (Murray and Chotirmall, 2015). In viral-driven pneumonia, immunosenescence causes a decrease in the diversity of the $CD8^+$ T cell compartment and in the global immune response to influenza infection (Zhang et al., 2002). In SARS-CoV-2 pneumonia, the total number of peripheral lymphocytes is reduced, displaying a clear defect in $CD8^+$ T cell abundance, shifting the $CD4^+$ to $CD8^+$ T cell ratio (F. Wang et al., 2020). Beyond alteration in abundance, it appears that the function of $CD8^+$ T cells in COVID-19 patients becomes exhausted (Zhang et al., 2019; Zheng et al., 2020). Immunosenescence also impairs B cell development at all stages, leading to a net reduction of the total numbers and diversity of immature B cells (Holodick and Rothstein, 2015). Consequently, the antibody specificity and antigen affinity are diminished, resulting in poor vaccination efficacy and susceptibility to lung infections in older people (Holodick and Rothstein, 2015). In SARS-CoV-2 pneumonia, the total number of peripheral B lymphocytes is reduced, a phenomenon that is reversed upon treatment (F. Wang et al., 2020). In the context of influenza infection, aged mice exhibit a defect in the cooperation between T follicular and B cells due to low expression of CD40L (Chen et al., 2020; Lefebvre et al., 2016). This is important because B cells require activation signalling through the CD40 receptor (by CD40L expressed in T cells) to undergo affinity maturation, class-switching, and differentiation into plasma cells (Chen et al., 2020; Lefebvre et al., 2016). Immunosenescence also induces B cell-intrinsic effects, such as low expression

of the transcription factors paired box 5 (Pax 5) and B-lymphocyte-induced maturation protein 1 (Blimp1), which are crucial for the development and differentiation of these B lymphocytes (Chen et al., 2020; Frasca et al., 2016; Nipper et al., 2018). Not too surprisingly, there is a poor production of influenza-neutralizing antibodies in aged mice, non-human primates and humans (Chen et al., 2020; Frasca et al., 2016; Josset et al., 2012; Toapanta and Ross, 2009). Collectively, immunosenescence affects the humoral immunity in the airways, creating an environment prone to infections and susceptible to other age-related pulmonary diseases.

1.3. Microbiota in the ageing lung

The microorganisms populating this tissue have a low density, which appears to be critical for the maintenance of healthy lungs (Mathieu et al., 2018) and these bacteria can exert distinct effect on the pathogenesis of lung diseases such as asthma (Mathieu et al., 2018; Remot et al., 2017). Due to the difficulty to access resident lung microbiota, to date, no study has been performed on lower respiratory tract microbiota in the elderly population and only few studies have compared the composition of the upper respiratory tract microbial ecosystem in the elderly to the one in younger adults (Table 1, (de Steenhuijsen Piters et al., 2016; J.-J. Lee et al., 2019; Stearns et al., 2015; Whelan et al., 2014)). Advanced age decreased the relative abundance of *Corynebacterium* and *Propionibacterium* in the nose and of *Prevotella* in the oropharynx. Importantly, Whelan *et al.* demonstrated that, although the microbiota from the anterior nares is distinct from that of the oropharynx in mid-aged adults, this distinction is abolished in elderly subjects (Stearns et al., 2015), suggesting that ageing in the upper airways is accompanied by a loss in the geodistribution of the microbial ecosystem. Another study by the same group, comparing URT microbiota from children to that of adults, reported similar high inter-individual variability, as was shown in elderly individuals. Therefore, it is possible that the absence of a more stable URT microbiota in these aged groups is related to a higher susceptibility to respiratory infections and other lung diseases, such as asthma as seen in children for whom the prevalence of these diseases is

also increased compared to adults. This is supported by mouse-based studies in which the age altered the recovery from pulmonary infection with *Streptococcus pneumoniae*. Indeed, older mice were less efficient to clear the pathogen and showed an increase in the abundance of OTUs from the *Firmicutes* phylum compared to the younger counterparts. The composition of URT microbiota from older mice also failed to return to their original composition, up to 4 weeks after the infection (Krone et al., 2014; Thevaranjan et al., 2016), suggesting a loss of resilience of their microbiota.

Table 1: Summary of the results of publications comparing respiratory tract microbiome from elderly to younger adults. Arrows indicate an increase (↗) or decrease (↘) in relative abundance of the microbiome

Study [ref]	N	Population	Age	Sample origin	Results	
Whelan (2014) (Whelan et al., 2014)	18	Elderly	68–96	Anterior nares and oropharynx	Elderly vs. mid-aged	No clustering based sample origin (anterior nares or oropharynx) in elderly ↗ *Streptococcus* (both locations) in anterior nares: ↘ *Corynebacterium, Propionibacterium, Staphylococcus* ↗ *Prevotella, Veillonella* in oropharynx: ↘ *Prevotella, Lachnospiraceae*
	242	Publicly available data (NIH's Human Microbiome Project)	18–40	Anterior nares and throats		
de Steenhuijsen (2016) (de Steenhuijsen Piters et al., 2016)	100	Elderly pneumonia (EP) patients	75.7	Oropharynx	HE *vs.* YH	↗ *Rothia* and *Lactobacillus* ↘ *Prevotella*, *Veillonella*, *Leptotrichia*,
	91	Healthy elderly (HE)	75.3		EP *vs.* HE & YP *vs.* YH	↗ overall bacterial density ↘ species richness (not in young cohorts) ↗ Shannon diversity indices (not in young cohorts) ↗ *Streptococcus* (*pseudo*)*pneumoniae*, several *Streptococcus* OTUs, *Rothia* ↘ *Gemellales*, *Prevotella melaninogenica*, *Veillonella dispar*, *Parascardovia* and *Leptotrichia*
	27	Young adult pneumonia (YP) patients	46.4			
	187	Young healthy adults (YH)	34.4			
Lee (2019) (J.-J. Lee et al., 2019)	10	Healthy elderly (HE)	67.3 ± 3.5	Nasopharynx	HE *vs.* HA	No change in diversity indices ↗ *Proteobacteria* ↘ *Propionibacterium*, *Corynebacteriales*
	30	Asthmatic elderly (AE)	72.5 ± 5.4		AE *vs.* AA	↘ *Staphylococcus*, *Propionibacterium*, *Moraxella*
	10	Healthy adults (HA)	25.4 ± 6.2		AA *vs.* HA	↗ *Proteobacteria*

	30	Asthmatic adults (AA)	34.1 ± 7.0		AE *vs.* HE	No significant relative abundances of phyla
Lee (2019) (S. Y. Lee et al., 2019)	24	Elderly	63	Sputum	Elderly *vs.* young	↗ *Firmicutes* ↘ *Proteobacteria* *Fusobacteria* and *Leptotrichia* associated with arterial stiffness in elderly subjects
	24	Young	29			

2. IMPACT OF NUTRITION ON AGEING/SENESCENCE AND ROLE OF THE MICROBIOTA

Lifestyle and more particularly certain diets/dietary patterns have been associated with changes in Years of Life Lost (YLL) and Years Lost due to Disability (YLD), thus modulating Disability-Adjusted Life Years (DALYs), which represents years of healthy life (GBD 2017 Diet Collaborators, 2019; May et al., 2015; Struijk et al., 2014).

2.1. Nutrition and cellular senescence

As described above, at the cellular level, the ageing process, called senescence is characterized, among others, by shortening of telomeres and the SASP (Senescence-Associated Secretory Phenotype). One current area of interest is whether diet can influence senescence process. This has now been studied by many groups and reviewed recently (Balan et al., 2018), although no consensus has emerged. Some studies have reported a positive association between a longer telomere length, measured in leukocytes, and certain types of food, including nuts, seaweed, fruits or coffee, whereas consumption of alcohol, and red or processed meat was associated with a shorter leukocyte telomere length (Balan et al., 2018; Lee et al., 2015; Leung et al., 2014; Liu et al., 2016; Pavanello et al., 2011; Tucker, 2018). Consumption of certain diets, foods and nutrients have also been positively or negatively associated SASP in different tissues (Sone and Kagawa, 2005; S.-Y. Wang et al., 2019; Yang et al., 2020). On the other hand, a meta-analysis from 2017 (Pérez et al., 2017), which included 533 participants under 9 different diets in 5 randomized controlled trials, showed that there was no effect of diet on telomere length. However, there was a high heterogeneity in the types, length of studies and in the dietary interventions, which might

have affected the conclusion of this meta-analysis. One of the hypotheses that could explain how diet impacts senescence process is through the regulation of ROS production and oxidative stress coming from endogenous and exogenous sources. Indeed, it is known, for example, that unhealthy diets, such as high fat diets, can induce an increase in ROS production in certain tissues (Matsuzawa-Nagata et al., 2008; Vial et al., 2011). Of interest, a healthy diet with reduced calorie intake (calorie restriction diet – CR), reduced mitochondrial activity and ROS production, and this has shown some promising results in certain studies. In animals, CR diet delayed the onset on some ageing-associated diseases such as diabetes (Cheng et al., 2017; Colman et al., 2009), cardiovascular diseases (Colman et al., 2009) or cancer (Weindruch et al., 1986), and it even prolonged life in non-human primates (Colman et al., 2014, 2009), although it did not appear to affect telomere length (Smith et al., 2011). In humans, while such studies are difficult to implement, similar health benefits have been reported in certain population, such as the Okinawan adult population. This population eats an average of 17% less calorie-intake compared to that of the rest of Japan, and has a higher rate of centenarian people and a lower mortality due to cardiovascular diseases, cancer and other diseases around the globe (Kagawa, 1978; Suzuki et al., 2001). The CALERIE 1 & 2 studies have also demonstrated the beneficial effect of a CR diet on general health and the prevention of ageing associated diseases (Most et al., 2018; Redman et al., 2018; Weiss et al., 2006). Interestingly, intermittent fasting has also been shown to reduce insulin resistance and cholesterol levels in humans, suggesting that this type of diet could also be beneficial against the development of ageing associated pathologies by modulating oxidative stress associated with ageing (Harvie et al., 2013, 2011; Klempel et al., 2012; Stekovic et al., 2019; Varady et al., 2015).

2.2. Involvement of the microbiota in the effect of nutrition on ageing processes

It is now widely accepted that the composition and function of the gut microbiota are clearly influenced by dietary intake and can be modulated by specific diets (*e.g.,* meat, vegetarians, rich in fiber) and the type of food matrices, which includes both the composition and

interactions between the constituents (Aguilera, 2019; David et al., 2014; Derrien and Veiga, 2017; Duncan et al., 2007; Ley et al., 2006; Muegge et al., 2011; Walker et al., 2011; Wu et al., 2011). Consequently, the effect of particular diets on molecular and cellular processes involved in ageing could be mediated by the modulation of microbiota.

2.2.1. Impact of nutrition on microbiota

Our diet feeds the microbiota by supplying substrates for microorganisms, especially non-digestible sugars, known as prebiotics (Gibson et al., 2017). Food is also a source of microorganisms, seeding our ecosystems in the gut and the lung. The overall microbial biomass ingested per day has been estimated around 10^{10} (Derrien and van Hylckama Vlieg, 2015), ranging from 10^{9} to 10^{12} in function of the diet considered. In addition to fermented foods, that are especially rich in microorganisms, it is important to realize that raw food we ingest (*e.g.,* fruits, vegetables) also contains their own microbial communities that could impact the composition and functionality of gut microbiota. Thus, modifying the diet for elderly people also impacts the microorganisms they ingest. Since the early 2010's, it is known that these food microorganisms survive through the GI tract and associate, at least temporarily, with the resident gut microbiota (David et al., 2014; Walker et al., 2011), although whether they "durably" colonize the digestive tract remains uncertain (McNulty et al., 2011).

Distinct types of food, such as non-digestible starch, and particular diets like the Mediterranean diet, affect the microbiota composition in a specific manner. It has been extensively reviewed in recent years (Barber et al., 2020; Burr et al., 2020; Dogra et al., 2020; Fassarella et al., 2020; Kolodziejczyk et al., 2019; Vandeputte and Joossens, 2020). Although there exists a very high inter-individual variability, due to host and microbe own characteristics, the microbiota appears as a strong malleable therapeutic target that can be reshaped using specific diets. For instance, a high-fat and low-fibre diet in mice decreased microbiota composition in *Bacteroidetes* and increased *Firmicutes* and *Proteobacteria* (Hildebrandt et al., 2009). The consumption of poly-unsaturated fatty acids increased

bacteria, such as *Bifidobacterium*, *Lachnospira*, *Roseburia* and *Lactobacillus*, in humans (Watson et al., 2018). Of interest for the ageing population as they often show protein deficiency, the source of this nutrient also affects the microbiota composition (Zhu et al., 2015). Soybean and peanut proteins induced modulation of the abundance of beneficial bacteria in the gut; a diet enriched with 20% peanut protein increased *Bifidobacteria*, and reduced *Enterobacteria* and *Clostridium perfringensa* in rats (Peng et al., 2015). On the other hand, animal derived proteins induced a *Bacteroides* enterotype (Wu et al., 2011). Gut bacteria can convert L-carnitine and phosphatidylcholine, which are present in red meats, into trimethylamine N- oxide (TMAO), which is associated with the development of cardiovascular diseases, linking, here as well, the impact of diet on microbiota and the host physiology. Strikingly, a recent study showed that in older individuals, consumption of Mediterranean diet was associated with specific changes in microbiota composition and function; adherence to this diet was associated with a lower decline in microbiota diversity, an increase in taxa negatively associated with inflammation and positively associated with SCFA production (Ghosh et al., 2020).

In addition to diet composition, food supplements or additives also impact gut microbiota composition. In recent years, studies have investigated the effect of probiotics - ingested as food supplements - or fermented foods, which both have a high microbial load, on the survival of these microorganisms their residence time in the host's digestive environment and their direct impact on the microbiota. Although fermented foods have shown to beneficially impact human health (Marco et al., 2017; Tamang et al., 2016), a detectable modification of the intestinal microbiota was not consistently observed in these studies, and it is therefore important to dissociate the direct effects of food microorganisms and associated bioactive compounds from those linked to the matrix itself. A recent study from Taylor *et al.* showed that, in stool samples from over 6000 individuals, there was a small significant change in beta diversity as well as differential taxa between people consuming fermented foods and non-consumers (Taylor et al., 2020). Finally, in one of the first reports on fermented foods effects on microbiota, McNulty *et al.* demonstrated the impact of these foods on the intestinal

physiology of an individual without necessarily modification of the composition of their microbiota (McNulty et al., 2011). Even though microbial food ecosystems might have very little influence on the diversity, composition and stability of the gut microbiota, they are thought to impact the host physiology.

Whether food, *via* substrates or microorganisms, is able to modify the lung microbiota is not known so far. A main trend of changes observed in gut microbiota in elderly populations is a decreasing abundance of beneficial microbes, like *Lactobacillus* and *Bifidobacterium*. Therefore, we assume that a diet enriched with these microorganisms or promoting their growth should be beneficial to counter-balance the loss. A better knowledge of the evolution of lung microbiota with age would help to define nutritional enrichment by specific microbes to preserve the lung microbiota.

2.2.2. Impact of microbiota on cellular senescence

As food modulates microbiota composition and function as well as molecular ageing processes, it is believed that one of the possible mechanisms of action of diets on ageing processes is through their action on microbiota, particularly the gut microbial ecosystem. This can occur through the metabolites they secrete or their interactions with the immune system and the epithelial barriers. Indeed, it has been shown that metabolites and secreted products from the microbiota are able to affect cellular senescence, either promoting or reducing it. In a healthy context, senescence can be detrimental, whereas in a carcinogenic context, for example, the induction of senescence can eliminate cancerous cells. For example, colibactin, a genotoxin from *E. coli*, has been shown to induce senescence, thus promoting colon tumor growth (Dalmasso et al., 2014). Other metabolites such as Cdtb (Cytolethal distending toxin subunit B) of *Helicobacter hepaticus*, Trimethylamine-N-oxide or Urolithin A can also induce senescence, although mechanisms of action vary from one metabolite to another (Giménez-Bastida et al., 2020; Ke et al., 2018; Péré-Védrenne et al., 2017). In the case of Urolithin A, it is of interest to note that the induction of senescence actually served to prevent irreversible, cell cycle progression of colon cancer cells. On the other hand, and of particular interest in

the search for molecules promoting healthy ageing, certain bacterial metabolites can also reduce or prevent senescent process. This is the case of secreted products from *Lactobacillus fermentum*, for example, which protects the 3T3-L1 preadipocytes *in vitro* against oxidative stress-induced senescence by inhibiting the mTOR pathway (Kumar et al., 2019). Although the responsible molecules have not been identified in this case, this study provided a *proof-of-concept* that metabolites from probiotics may possess anti-ageing properties. Depending on the diet and type of food intake, gut microorganisms can also produce a family of metabolites termed short-chain fatty acids (SCFA). These are end products of bacterial fermentation that happens in the gut and play important roles at local and distant sites. In 2012, O'Callaghan *et al.* showed that a red meat rich diet was linked to a decreased telomere length in rat colonic cells and could be prevented by adding resistant starch to the diet. Interestingly, they found an association between the absolute telomere length and the caecal levels of two SCFAs, acetate and propionate (O'Callaghan et al., 2012).

It is now well established that the gut microbiome plays an important role in the development and maturation of the immune system throughout life. In healthy individuals, commensal bacteria rarely cross the physical barrier constituted by the epithelial cells and the mucus layer. However, when this happens, bacteria are rapidly killed by macrophages. Others can survive inside DCs but these cells only go as far as the mesenteric lymph nodes, restricting the bacterial challenge to the mucosal immune system (Macpherson and Uhr, 2004). As the epithelium becomes leaky with age, it is inferred that more commensals or bacterial components can cross that barrier and may induce aberrant immune responses (Man et al., 2014; Thevaranjan et al., 2017). The immune system may then react against native microflora as well as inappropriately control invading pathogens. Additionally, the decline in gut microbiota diversity, observed in older individuals, may also impact the immune system at the local and systemic levels. This could be due, at least partly, to the reduction in growth control of distinct groups of potentially pathogenic bacteria. Together, this may participate in

410 the establishment of the low-grade inflammation observed in ageing individuals (Rehman,
411 2012), as well as the onset of age-related illnesses.
412 Taken together, these studies show that diets modulate molecular mechanisms involved in
413 ageing through their actions on gut microbiota. Thus, in older people, nutrition represents a
414 mean of action to maintain a balanced gut microbiota that will positively impact senescence
415 and ageing, at the local and systemic levels.
416

417 **3. THE GUT-LUNG AXIS AND AGEING LUNGS**

418 In the literature, the first papers supporting the existence of an intestine-lung axis, trace back
419 to the early 1990's and referred to the occurrence of ARDS (Acute respiratory distress
420 syndrome) following septic shock and translocation of bacterial products from the lumen of
421 the intestine to the blood stream (Pugin and Chevrolet, 1991). It was actually mainly known
422 as the gut-liver-lung axis as the ARDS was caused by degranulation of neutrophils that was
423 triggered by inflammatory factors secreted by the liver (Pugin and Chevrolet, 1991). Using a
424 bone marrow transplantation mouse model, Cooke *et al.* later proposed that controlling gut
425 toxicity and specifically the translocation of lipopolysaccharide (LPS) across the intestinal
426 epithelium could reduce idiopathic pneumonia syndrome, demonstrating the existence of a
427 gut-lung axis of inflammation (Cooke et al., 2000). It is now known that certain acute and
428 chronic lung diseases are associated with dysbiotic microbial communities in the lung and
429 gut, and with gut symptoms or disorders. This relationship is bi-directional and, although
430 evidence for the lung-gut axis is not as abundant as data on the gut-lung axis, it is now well
431 established that chronic and acute lung disease induce changes in the gut microbiology and
432 physiology. One of the striking recent evidence supporting this is the presence of
433 gastrointestinal symptoms in 10 to 18 % of patients infected by the SARS-CoV-2, according
434 to the most recent meta-analyses (Trottein and Sokol, 2020), for which, although all age
435 groups can contract the virus, older people (60+) are at increased risk of developing severe
436 illness. Here, we present the physiological similarities between the two tissues, and the

anatomical features enabling the gut-lung axis, and review the evidence of the reciprocal regulation of the microbial ecosystems and epithelial physiology between the airways and the gastrointestinal (GI) tract.

3.1. The anatomical continuum between the lungs and gut is more permissive to exchanges in the elderly

In the gut and lungs, the epithelium serves a crucial role of barrier that is at the same time, physical, chemical and physiological. Interestingly, the permeability of both the lung and gut epithelia is increased in aged individuals or ageing animal models (César Machado and da Silva, 2016; Parrish, 2017; Tankersley et al., 2003), suggesting an impaired barrier function of these tissues with old age. These structures are in permanent contact with exogenous particles and microorganisms with a potential for pathogenicity and by regulating their permeability through their tight junctions; they allow selective transfer of materials across this physical barrier. They also take part in the innate immune response to pathogens, acting as a chemical barrier, by secreting soluble factors that will either have antimicrobial activity (direct response) or signal to the immune system their presence, and thus trigger the appropriate innate and adaptive immune responses. Both epithelial structures are also able to tightly regulate ion and fluid transport *via* the expression of many ion channels and transporters common to both organs, which are of particular importance in the regulation of the composition and pH of the luminal environment in which the microbiota live. These barriers become ‘leakier’ with age, but up to now there is no evidence this is a cause or consequence of microbiota dysbiosis. However, it is plausible that an impaired epithelial barrier would allow for less stringent regulation of the trans-epithelial transport of microbes and microbial metabolites, and therefore an enhanced and unfiltered communication along the gut-lung axis that would lead to a loss in compartmentalisation of the microbiota.

Moreover, microbiota from the gut, the nose and throat, have recently been shown to develop in a coordinated way during the first year of life (Grier et al., 2018). Both the GI and

464 respiratory tracts share a common entry point for microorganisms – the oral cavity. In this
465 organ, the microbiota has been shown to share significant overlaps with both the gut and
466 lung ecosystems (Bassis et al., 2015; Segata et al., 2012), and it is able to modulate
467 inflammation in bronchial cells *in vitro* (Mathieu et al., 2020). A study from the Human
468 Microbiome Project revealed a 45 % overlap between the microbiota from the oral cavity and
469 stool samples (Segata et al., 2012). Interestingly, Bassis *et al.* demonstrated that, using
470 redundancy analysis of the microbiota from the mouth, nose and broncho-alveolar lavage
471 (BALs), the microbial community from the BALs were closer to that of the mouth instead of
472 that found in the nose, although the indices of intra-subject similarity ranged from dissimilar
473 to highly dissimilar. When looking at bacterial Operational Taxonomic Units (OTUs), the
474 bacterial communities of the lung showed a significant overlap with the ones from the mouth,
475 but they differed considerably from those found in the nose (Bassis et al., 2015). Therefore,
476 this establishes an anatomical continuum for microorganisms from the mouth to colonize
477 both the respiratory and GI tracts (Figure 3). Microorganisms from the mouth migrate to the
478 GI tract by swallowing, whereas they colonize the lungs through micro-aspirations and
479 inhalation of micro-aerosols. The elimination of microorganisms from the lungs occurs *via* the
480 mucociliary escalator, in which the coordinated movement of the cilia together with the
481 secretion of mucus, ion and water, allows to move the mucus up towards the pharynx, where
482 it will be swallowed or expectorated. By contrast, microbes present in the stomach may move
483 back to the mouth *via* the oesophagus in cases of gastroesophageal reflux and be inhaled in
484 the lungs. This is supported by the fact that the composition of the lung microbiome more
485 closely resembles that of the oropharynx than the nasopharynx (Bassis et al., 2015; Dickson
486 and Huffnagle, 2015). Additionally, a study by Rosen *et al.* showed that the concentration of
487 some bacteria in the lung was correlated with full-column non-acid reflux burden in patients
488 receiving acid-suppression therapy, supporting the fact that gastric microbiota can alter lung
489 microbiota (Duvallet et al., 2019; Rosen et al., 2014). The prevalence of gastroesophageal
490 reflux disease increases with age (Poh et al., 2010; Zhu et al., 1993), suggesting that transfer
491 of microbiota from the stomach to the lungs might happen more easily in older individuals,

492 providing here as well, an enhanced and unchecked communication pathway between the
493 gut and the lung. Moreover, some studies have shown that the coordinated response to
494 certain stresses or pathogens in the lungs and the gut are mediated through the modulation
495 of the immune system and the transport, in the blood, of bacterial metabolites (Figure 3).

496 *3.2. From the lungs to the gut – impact of lung infections on gut health*

497 Although it is difficult to establish a causal link between certain lung diseases and a dysbiotic
498 gut microbiota in humans, animal models have strongly contributed to this field in recent
499 years. The pioneering work from Sze *et al.* demonstrated that, in mice, acute lung injury
500 induced by LPS caused an increase in bacterial load in the blood and caecum, whereas lung
501 total 16S was slightly reduced in BALs and changes in abundance of certain bacterial
502 species occurred (Sze et al., 2014). Another model of lung injury in mice, induced by
503 cigarette smoke, further detailed the impact of acute exposure to stress on gut inflammation,
504 and it identified the Th17-dependent pathway as a main player in the communication
505 between the two tissues (Kim et al., 2019). In this study, mice were exposed to cigarette
506 smoke and then to an intestinal inflammatory challenge (2 % DSS in drinking water for 6
507 days). DSS-induced weight loss was more pronounced in mice exposed to cigarette smoke,
508 and this was accompanied by increased histological damage and immune cell infiltration at
509 the intestine level (Kim et al., 2019). This study did not report on the composition of the lung
510 and gut microbiota. However, it is possible that cigarette smoke-induced changes in the lung
511 microbial community that drove the local and systemic immune responses.
512 Of interest, especially in elderly people, is the impact of respiratory infections on gut
513 microbial and physiological homeostasis. As previously mentioned, older people are at
514 higher risk of complications when infected by certain respiratory viruses or bacteria (see
515 chapter 2). To date, no study has specifically reported the effect of respiratory bacterial or
516 viral infections on the gut microbiota in older human populations. However, studies in
517 younger human populations and in mouse models have provided accumulating evidence

518 supporting a central role for acute infections in modulating gut microbiota and impacting its
519 homeostasis (Table 2).

520

521 **Table 2: Impact of respiratory pathogens on gut microbiota, mechanisms of action and consequences.**
522 Arrows indicate an increase (↗) or decrease (↘) in relative abundance of the microbiome

523

Study [ref]	Animal / Microbiota Analysis method	Infectious agent	Effect on gut microbiota	Mode of Action and consequences
Viruses				
Wang (2014) (Wang et al., 2014)	Mouse / Real-time PCR and selective culture	Influenza A/PR/8/34 (PR8), 0.1 HA of PR8, intranasally	No change in number of total bacteria ↘ *Segmented filamentous bacteria* (SFB) ↘ *Lactobacillus/Lactococcus* ↗ *Enterobacteriaceae* (*E. coli*)	Lung-derived $CD4^+$ T cells -> IFN-γ CCL25-CCR9 axis: recruitment of $CCR9^+CD4^+$ cells to the intestine -> gut microbiota dysbiosis
Qin (2015) (Qin et al., 2015)	Human / Illumina TruSeq	H7N9	↗ *Proteobacteria* ↘ *Eubacterium*, *Ruminococcus*, *Bifidobacterium* and *Roseburia* ↗ *Escherichia*, *Salmonella*, *Enterococcus*, *Veillonella*	N/A
Yu (2015) (Yu et al., 2015)	Mouse / Bacterial colony plate counts	Influenza A/FM1/1/47 20% Lethal Dose 50 intranasally	↘ *E. coli* ↘ Anaerobic bacteria ↗ *Bifidobacterium* and *Lactobacillus*	N/A
Deriu (2016) (Deriu et al., 2016)	Mouse / MiSeq Illumina	Influenza A /Puerto Rico/8/34 (PR8) – 200 PFU – intra-tracheal	↗ *Proteobacteria* ↗ *Escherichia*	↗ IFN-Is ($Ifnar1^{-/-}$) mice IAV leads to enhanced susceptibility to secondary enteric infections
	Mouse / 16S qPCR		↗ *Enterobacteriaceae* ↘ *Segmented Filamentous Bacteria*	N/A
Bartley (2017) (Bartley et al., 2017)	Mouse / Miseq Illumina	Influenza virus A/PR/8/34 (PR8), 400 EID50 intranasally	↗ *Proteobacteria* ↗ *Verrucomicrobia*	N/A
Groves (2018) (Groves et al., 2018)	Mouse / MiSeq Illumina	RSV-A2, 2×10^5 PFU/ml	No change in total fecal bacterial load, total observed OTU, alpha diversity ↗ *Bacteroidetes* (*Bacteroidaceae*) ↘ *Firmicutes* (*Lachnospiraceae*, *Lactobacillaceae*)	↗ in MUC5AC provides a source of energy to *Bacteroidetes*
	Mouse / MiSeq Illumina	Influenza A/Eng/195/2009, 4×10^4 PFU/ml	↗ *Bacteroidetes* (*Porphyromonadaceae*) ↘ *Firmicutes*	N/A
Yildiz (2018) (Yildiz et al.,	Mouse /	Influenza A/Viet Nam/1203/2004,	Transient decrease in community richness in small intestine at 7dpi	IAV leads to enhanced susceptibility to secondary enteric

2018)	MiSeq Illumina	intranasal	↘ *Firmicutes* in small intestine at 7dpi ↘ *Bacteroidetes* in small intestine at 7dpi No change in fecal bacteria	infections
Sencio (2020) (Sencio et al., 2020)	Mouse (C57BL/6J) / • MiSeq Illumina	• Influenza H3N2 IAV Scotland/20/1974, 30 pfu, intranasally • Influenza H1N1 WSN/1933, 200 pfu, intranasally • Influenza H1N1 California/04/2009, (pdm09), 100 pfu intranasally	↗ *Verrucomicrobia* (*Akkermansia*), *Cyanobacteria* ↗ *Parabacteroidetes* and *Odoribacter* ↘ *Bacteroidales* S24-7 ↗ *Clostridiales* (unaffiliated), *Ruminococcaceae*, and *Mogibacteriacecea* ↘ *Lachnospiraceae* family, *Dehalobacterium* and *Lactobacillus* genera ↗ *Alphaproteobacteria* *Gammaproteobacteria* (*Escherichia* genus) ↘ *Betaproteobacteria* (*Sutterella* genus)	IAV infection leads to decreased food intake, less production of Short chain fatty acids, particularly acetate
Bacteria				
Mycobacterium tuberculosis				
Winglee (2014) (Winglee et al., 2014)	Mouse (Balb/c) / 454 FLX pyro-sequencing	*Mycobacterium tuberculosis* CDC1551 or H37Rv,, aerosol (Middlebrook inhalation exposure system)	↘ Diversity ↘ *Bacteroidetes* ↗ *Actinobacteria* ↗ *Lactobacillus* ↘ *Lachnospiraceae* ↘ *Ruminococcaceae*	N/A
Luo (2017) (Luo et al., 2017)	Human (adults) / MiSeq Illumina		↘ *Bacteroidetes* ↗ *Proteobacteria* (*Escherichia*), *Actinobacteria* (*Collinsella*) ↘ *Prevotella*, *Lachnospira*, *Roseburia*, *Coprococcu* (*Firmicutes*)	N/A
Hu (2019) (Yongfei Hu et al., 2019)	Human (adults) / HiSeq 2500 Illumina	*Mycobacterium tuberculosis*	↘ Alpha-diversity ↗ *Coprobacillus bacterium* and *Clostridium bolteae* ↘ *Haemophilus parainfluenzae, Roseburia inulinivorans, Eubacterium eligens, Roseburia hominis, Roseburia intestinalis, Megamonas unclassified, Eubacterium rectale, Ruminococcus obeum, Dora formicigenerans, Coprococcus sp_ART55/1, Megamonas funiformis, Sutterella wadsworthensis, Bifidobacterium adolescensis, Megamonas hypermegale, Collinsella aerofaciens, Bifidobacterium longum, Akkermancia muciniphila, Megamonas rupellensis, Coprococcus comes, Lachnospiraceae bacterium*	N/A

			1_1 57FAA, *Ruminococcus lactaris*, *Bifidobacterium pseudocatenulatum*, *Dorea longicatena*	
Hu (2019) (Yongfeng Hu et al., 2019)	Human (adults) / HiSeq 2500 Illumina	*Mycobacterium tuberculosis*	No significant difference	N/A
Huang (2019) (Huang et al., 2019)	Human (adults) / MiSeq Illumina	*Mycobacterium tuberculosis*	↗ *Bacteroidetes* ↘ *Bifidobacteriaceae*	Correlation between gut F/B ratio blood IL-1β
Li (2019) (Li et al., 2019)	Human (children) / MiSeq Illumina	*Mycobacterium tuberculosis*	↘ Diversity (Simpson index) ↗ *Enterococcaceae*, *Prevotellaceae* ↘ *Rikenellaceae*, *Bifidobacteriaceae*, *Lachnospiraceae*, *Ruminococcaceae*, ↗ *Enterococcus*, *Prevotella* ↘ *Faecalibacterium*, *Bacteroides Ruminococcus*, *Dorea*	N/A
Namasivayam (2019) (Namasivayam et al., 2018)	Rhesus macaques / Illumina NextSeq (V4 region)	*Mycobacterium tuberculosis* Erdman strain, <10 CFU, intrabronchial instillation	Minor changes Severe diseases associated with: ↗ *Roseburia intestinalis* (family *Lachnospiraceae*), *Succinivibrio dextrinosolvens*, certain *Ruminococcaceae*, and *Weissella* (family *Leuconostocaceae*) ↘ *Streptococcus equinus* (family *Streptococcaceae*)	N/A
Streptococcus pneumoniae				
Dabrowski (2019) (Dabrowski et al., 2019)	Mouse (BALB/c) / MiSeq Illumina	*Streptococcus pneumonia*, NCTC 7978, 10^5 cfu	↗ *Lachnospiraceae*, *Ruminococcaceae* ↘ *Bacteroidales* S24-7, *Lactobacillaceae*, *Coriobacteriaceae*	N/A
Fungi				
Samuelson (2016) (Samuelson et al., 2016)	Mouse (C57BL/6j) / MiSeq Illumina	*Pneumocystis murina* (2×10^6 cysts/mL (intratracheal)	↘ α-diversity ↗ *Lactobacillus*, *Ruminococcus bromii* ↘ *Turicibacter*, *Lachnospiraceae* *Oscillospira*,	N/A

Of note, respiratory pathogens, however diverse they are, trigger common shifts in microbiota composition; species from the *Firmicute* phylum and *Clostridiales* order, including *Lachnospiraceae*, *Faecalibacterium* and *Ruminococcus*, are generally decreased as are *Bifidobacteria* from the *Actinobacteria* phylum. By contrast, *Proteobacteria*, especially *E. coli* species are found increased in the gut of individuals or animals infected with respiratory

pathogens. As studies are sparse for certain types of pathogens such as fungi or certain bacteria commonly responsible for pneumonia in elderly people, it is, at the time of writing, impossible to identify specific patterns associated with specific types of pathogens.

Most studies that have searched for gut colonization of the respiratory pathogen have not found any evidence that this occurs, suggesting that there exist other lines of communication responsible for the dysbiosis observed in the gut. Mechanisms of action involved in transducing the signal of infection from the lungs to the GI tract are not yet fully understood, although certain pathways have been identified. For instance, Wang *et al.* showed that after Influenza A virus (IAV) infection, lung-derived $CD4^+$ T cells activate the CCL25-CCR9 axis to induce the recruitment of $CCR9^+CD4^+$ T cells to the intestine and thus inducing gut microbiota dysbiosis. Likewise, a recent study by Liu *et al.* showed that mast cells might also be key players in transducing the signal of infection from the lungs to the gut (Liu et al., 2019).

3.3. From the gut to the lungs – Impact of gut microbiota and food intake/diet on lung health

As previously described, respiratory infections can impact the composition and diversity of gut microbiota either by modulating local immune populations that are then recruited to the gut, or by inducing anorexia, thus decreasing food intake and nutrient availability. Interestingly, these changes in microbiota feed back to the respiratory tract and increase the susceptibility to secondary infections, as in the case of Influenza virus infections (Sencio et al., 2020). There are now multiple reports supporting the role of intestinal microbiota in the maintenance of healthy lungs, as well as its responses to respiratory infections and vaccines (Dumas et al., 2018; Hanada et al., 2018). Many studies have used oral antibiotics administration in order to investigate the role of gut microbiota in other tissue responses to various stressors (*e.g.* infection, inflammation). However, the impact of such treatment on distal microbiota such as the pulmonary microbiota has rarely been investigated and thus requires further exploration. For example, early studies demonstrated that antibiotics

557 treatment increased mortality of animals that were infected with IAV (Abt et al., 2012;
558 Ichinohe et al., 2011) or *S. pneumoniae* (Schuijt et al., 2016). Although the effect of oral
559 antibiotics on lung microbiota cannot be excluded, several studies have reported different
560 means of communication between the gut and the lungs. This communication along this gut-
561 lung axis can be mediated by (i) the immune system, (ii) transfer of microbes, or (iii) microbial
562 and host metabolites in the blood from one tissue to the other. Since the gut microbiota plays
563 a major role in shaping the immune system, it affects both local and systemic (in the lungs)
564 responses to pathogens.

565 *3.3.1. Communication via the immune system.*

566 Depleting gut microbiota with antibiotics modulated the degree of the macrophage response
567 to respiratory IAV infection by decreasing the expression of macrophage-associated antiviral
568 response genes in these circulating leukocytes, particularly genes related to IFN-dependent
569 responses (Abt et al., 2012). Schuijt *et al.* also reported that alveolar macrophages and
570 whole-blood neutrophils displayed a decreased phagocytic activity against *S. pneumoniae*,
571 and a decreased inflammatory profile in response to stimulation with TLR ligands (Schuijt et
572 al., 2016). Interestingly, in the latter study, faecal transfer of a microbiota from healthy
573 animals restored pulmonary bacterial clearance and certain cytokines levels in the lungs
574 (Schuijt et al., 2016). Another study reported the pivotal role of Granulocyte-macrophage
575 colony-stimulating factor (GM-CSF) and IL-17A in the bacterial clearance of *S. pneumoniae*
576 and *Klebsiella pneumoniae*. Both cytokine levels were impacted by oral antibiotics
577 administration and neutralising antibodies increased bacterial burden in non-antibiotic-treated
578 mice. Moreover, by orally or intra-nasally administering a consortium of bacteria that were
579 strong Nod2 activators, it was shown that the restitution of either microbiota could rescue
580 defects in pulmonary clearance of *S. pneumoniae* or *K. pneumonia* (Brown et al., 2017). In
581 the case of viral infections with IAV, Ichinohe *et al.* demonstrated that antibiotics treatment
582 altered B cells, $CD4^+$ and $CD8^+$ T cells, as well as DC homeostasis; mediastinal lymph nodes
583 DC numbers were reduced and showed an impaired presentation of viral antigen peptide,

584 making them unable to activate antigen specific $CD8^+$ T cells (Ichinohe et al., 2011). Finally,
585 Gauguet *et al.* showed that gut microbiota also impacts responses to pulmonary infections by
586 modulating the Th17 cell-mediated immunity. Particularly, they found that the presence of the
587 commensal segmented filamentous bacteria (SFB) in murine GI tract protected against
588 Methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia and increased mucosal
589 immunity (specifically type-3 immune effectors) in the lung. This was linked to higher levels of
590 IL-22 and larger numbers of IL-22^+TCRβ^+ cells in BAL fluids (Gauguet et al., 2015). Taken
591 together, these studies demonstrate that gut microbiota can impact innate and adaptive
592 immunity by allowing the trafficking of immune cells between the gut and the lungs, which
593 further modulate responses to respiratory pathogens. This suggests that this axis of
594 communication, if functional, might play a beneficial role in the fight against pulmonary
595 bacterial and viral infections. We infer that altered microbiota in the ageing gut decreases its
596 protective role.

597 *3.3.2. Communication via soluble components and metabolites.*

598 In addition to directly modulating the host immune system, the microbial ecosystems also
599 produce soluble mediators that can be detected by the host. This is the case of SCFA, which
600 have been shown, in several studies, to exert a crucial role in shaping the local (gut) immune
601 system (reviewed in (Parada Venegas et al., 2019)). The three major SCFAs are butyrate,
602 propionate and acetate, and these have been shown to exert positive effect against
603 respiratory tract infections. Specifically, in 2018, Trompette and colleagues showed that upon
604 reaching the bone marrow, butyrate increased the production of a certain subtype of
605 macrophages (Ly6c$^-$) that decreased the recruitment of neutrophils in the mouse lungs. In
606 parallel, the SCFA also increased $CD8^+$ T cell effector function, and together these protected
607 the animals against Influenza virus lung damage (Trompette et al., 2018). Interestingly, Haak
608 *et al.* showed that in patients that had received allogenic hematopoietic stem cell
609 transplantation, a high abundance of butyrate-producing bacteria in faecal samples was
610 associated to a decreased risk of developing viral lower respiratory tract infections (LRTI)

(Haak et al., 2018). The effect of butyrate is not specific to viruses as it was effective in increasing survival of mice infected with *K. pneumonia*e (Chakraborty et al., 2017). Acetate protected mice against Respiratory syncytial virus (RSV) infection as observed by a lower weight loss, and a decreased lung viral load and inflammation (Antunes et al., 2019). Galvao *et al.* also demonstrated that acetate, *via* the activation of its receptor, free fatty acid receptor 2 (FFAR, also known as GPR43), was protective against *K. pneumoniae* infection also by controlling bacterial load and inflammation levels (Galvão et al., 2018). Finally, the study by Sencio *et al.* also reported that acetate protected against secondary lung infections. This group primarily infected mice with IAV followed by a secondary pulmonary infection with *S. pneumoniae*. They found that supplementation with acetate restored IAV-induced impairment of alveolar macrophages bacterial killing activity as well as prolonged mice survival following bacterial infection (Sencio et al., 2020). Taken together, these studies demonstrate the protective function of gut microbial metabolites against respiratory infection.

The evidence of this Gut-Lung axis has led to the hypothesis that respiratory infections might be prevented, or at least dampened, by modulating the intestinal microbial ecosystem through changes in food intake or supplementation with pre- and probiotics. Particular diets have been associated, in animal models as well as in humans, with either the exacerbation or the improvement of lung health in acute and chronic diseases. Particularly, fiber-rich diet has been associated with lower risk of developing COPD (Vaughan et al., 2019), improved response to viral infection (Trompette et al., 2018), and decreased severity of allergic airway disease (Trompette et al., 2014). It has been shown that probiotics can impact the course of respiratory diseases. Using a mouse model and the probiotic *Lactobacillus plantarum* CIRM653, Vareille-Delarbre reported a reduced response to intra nasal infection with *K. pneumonia* (Vareille-Delarbre et al., 2019). Results from randomised control trials and meta-analyses generally show improvement of lung health following probiotics supplementation, whether it impact the incidence of certain infections, the duration, or the severity of the disease (de Vrese et al., 2006; Hao et al., 2015; Wang et al., 2016).

4. DISCUSSION

As described in this review, recent studies have provided evidence for the modulation of respiratory health by diets and/or shifts in microbiota composition and function (Sencio et al., 2020; Trompette et al., 2018, 2014; Vaughan et al., 2019). These studies have mainly been carried out on animal models at a young or adult age. The ageing process is influenced by both intrinsic and external factors. In addition to replicative senescence, events along people's lifespan might have long-lasting impacts on their own physiology, as well as on their microbiota. Repetitive courses of antibiotics, for example, disrupt the gut microbial ecosystem, and we can assume that it is also the case for the lung microbiota. Considering the physiological characteristics of the elderly population, it is now important to investigate the interactions between diet, gut and lung microbiota, and lung health and disease, in models mimicking more closely the physiological changes happening in older human adults. This would involve either aged wild-type animals or genetically modified animal models of accelerated ageing. The *Terc*$^{-/-}$ mice, for example, are deficient in the RNA subunit of the telomerase, and have shown a higher susceptibility to bacterial pneumonia (Kang et al., 2018), while the *Klotho*$^{-/-}$ mice, which develop premature-ageing syndrome, also develop emphysema (Nakatani et al., 2009). It also appears that the lines of communication between the gut and the lungs might be enhanced by the impairment of the barrier function of both epithelial structures. Establishing models that will mimic these features will allow the study of the impact of the loss of topography of the microbiota in the susceptibility and pathogenesis of pulmonary diseases. Interestingly, a loss of compartmentalisation of the microbiota has been reported in chronically malnourished children (Vonaesch et al., 2018). Extrapolating to elderly individuals, malnutrition could also lead to the loss of topography of the microbiota, exacerbating the communication between the lung and the gut and thus increasing the susceptibility to respiratory diseases. Although mammalian lungs from different species share extensive characteristics, there exist differences, particularly between rodents and humans, which can impact responses to inhaled particles and pathogens. This is particularly

the case for ion channels and transporters that actively participate in the mucociliary escalator to remove particulate matter trapped in the mucus, and are therefore playing a central role in the barrier function of the airway epithelium (Cutting, 2015; Tanner and Beeton, 2018). Consequently, although difficult to implement, it will be crucial to further investigate the impact of diet, probiotics and prebiotics on respiratory health in human older adults. Thus, investigating the regulatory pathways between what we eat and how we breathe, will not only expand the basic knowledge and understanding of the gut-lung axis, but it will also help develop nutritional strategies to prevent the development of respiratory pathologies in the elderly.

Older individuals are often malnourished; dietary needs evolve with age while nutrient intake does not always change appropriately. It is thus critical to optimize nutrient intake and adapt food matrices in order to elaborate personalized diets allowing the maintenance of adequate nutritional health. In addition, as elderly people present dysbiotic microbiota, it appears necessary to provide food supplements that will restore microbial balance (Figure 4). These supplements can be probiotics, prebiotics or synbiotics, a combination of prebiotics with probiotics that improve the survival and implantation of the microorganisms in the GI tract (de Vrese and Schrezenmeir, 2008). It is now essential to confirm the emerging evidence of the impact of specific diets and supplements on respiratory health that suggests that nutrition may be the most accessible lever of action to prevent the development of lung diseases. The potential use of microbiota in clinical applications for preventing lung pathologies in older populations is of particular interest.

It is well known that viral respiratory infections such as influenza, SARS or RSV, can cause serious illness in elderly patients and are often associated with changes in gastro-intestinal homeostasis and gut dysbiosis. Strikingly, older patients infected with SARS-CoV-2 who were hospitalized, frequently presented comorbidities, with hypertension and T2D being amongst the most prevalent ones (Guan et al., 2020; Richardson et al., 2020). These two conditions have also been associated with gut dysbiosis (Gurung et al., 2020; J. Li et al., 2017) and taken together, this points out to a central role of the microbiota in the physiology

of the elderly and the pathophysiology and disease course of airway diseases. As clinical studies have shown that probiotics can decrease the duration and severity of symptoms of respiratory viral infections (de Vrese et al., 2006), we argue that developing personalized nutritional plans specifically reinforcing a symbiotic microbiota will help in the fight against respiratory pathogens (Figure 4).

CONCLUSIONS

Older age is associated with dysbiotic gut and lung microbiota along with a loss of resilience and compartmentalisation of microbial species in both tissues. In this review article, we propose the existence of an enhanced bidirectional communication between the gut and the lung, which could link the nutritional status to the susceptibility to respiratory diseases in older individuals. Collectively, the studies presented here highlight a central role for the gut-lung axis and the corresponding local microbiota communities in the maintenance of healthy lungs in older individuals.

LIST OF ABBREVIATIONS

AECII: Alveolar epithelial type II cells

AMDC: airway mucosal DC

ARDS: acute respiratory distress syndrome

ATP: adenosine triphosphate

BAL: bronchoalveolar lavage

BCR: B cell receptor

Blimp: B-lymphocyte-induced maturation protein

CAF: cancer-associated fibroblast

718 CAP: Community Acquired Pneumonia

719 COPD: Chronic Obstructive Pulmonary Disease

720 COVID-19: coronavirus disease 2019

721 CR: Calorie restriction

722 Cx43: connexin 43

723 DALY: Disability-Adjusted Life Years

724 DC: Dendritic cell

725 DDR: DNA damage response

726 DKC1: dyskerin 1

727 ECM: extracellular matrix

728 ER: endoplasmic reticulum

729 ERS: European Respiratory Society

730 EV: extracellular vesicles

731 FFAR: Free fatty acid receptor

732 FOXO: forkhead box “O”

733 GATA4: GATA binding protein 4

734 GI: gastrointestinal

735 GM-CSF: Granulocyte-macrophage colony-stimulating factor

736 IAV: influenza A virus

737 IFN: interferon

738 Ig: immunoglobulin

739 IGF-1: insulin-like growth factor 1

740 IIS: insulin and IGF-1 signaling

741 IL: interleukin

742 IPF: Idiopathic Pulmonary Fibrosis

743 IRP2: iron-regulatory protein

744 LPS: ipopolysaccharid

745 LRTI: lower respiratory tract infections

746 MHC: major histocompatibility complex

747 miRNA: microRNA

748 MRSA: Methicillin-resistant Staphylococcus aureus

749 mTOR: mammalian target of rapamycin

750 NET: neutrophil extracellular trap

751 NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells

752 NO: nitric oxide

753 NSCLC: non-small cell lung cancer

754 OTU: Operational Taxonomic Units

755 Pax: paired box

756 PI3K: phosphoinositide 3-kinase

757 PINK1: PTEN-induced putative kinase I

758 PTEN: phosphatase and tensin homolog

759 ROS: reactive oxygen species

760 RSV: Respiratory syncytial virus

761 SAMP: senescence-accelerated prone

762 SAMR: senescence-accelerated resistant

763 SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

764 SASP: senescence-associated secretory phenotype

765 SCFA: short-chain fatty acids

766 SFB: segmented filamentous bacteria

767 SP: surfactant protein

768 T2D: Type 2 Diabetes

769 Tc: cytotoxic effector T cell

770 TCR: T cell receptor

771 TGF: Transforming growth factor

772 TLR: toll-like receptor

773 TNM: tumor, node, metastasis

774 Treg: regulatory T cell

775 UPR: unfolded protein response

776 URT: upper respiratory tract

777 WHO: World Health Organization

778 YDL: Years Lost to Disability

779 YLL: Years of Life Lost

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DECLARATIONS

Declaration of Competing Interests

None of the authors of this paper have a financial or personal relationship with people or organizations that could inappropriately influence or bias the content of the paper.

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CRediT authorship contribution statement

Vinciane Saint-Criq: Conceptualization, Writing - original draft, Writing - review & editing; **Geanncarlo Lugo-Villarino:** Writing - original draft, Writing - review & editing, Funding acquisition; **Muriel Thomas:** Conceptualization, Writing - review & editing, Funding acquisition. All co-authors actively contributed to the critical discussions. All co-authors read and approved the final manuscript.

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REFERENCES

Abt, M.C., Osborne, L.C., Monticelli, L.A., Doering, T.A., Alenghat, T., Sonnenberg, G.F., Paley, M.A., Antenus, M., Williams, K.L., Erikson, J., Wherry, E.J., Artis, D., 2012. Commensal bacteria calibrate the activation threshold of innate antiviral immunity. Immunity 37, 158–170. https://doi.org/10.1016/j.immuni.2012.04.011

Agrawal, A., Agrawal, S., Cao, J.-N., Su, H., Osann, K., Gupta, S., 2007. Altered innate immune functioning of dendritic cells in elderly humans: a role of phosphoinositide 3-kinase-signaling pathway. J. Immunol. 178, 6912–6922. https://doi.org/10.4049/jimmunol.178.11.6912

Agrawal, A., Gupta, S., 2011. Impact of aging on dendritic cell functions in humans.

808 Ageing Res. Rev. 10, 336–345. https://doi.org/10.1016/j.arr.2010.06.004

809 Aguilera, J.M., 2019. The food matrix: implications in processing, nutrition and health.
810 Crit Rev Food Sci Nutr 59, 3612–3629.
811 https://doi.org/10.1080/10408398.2018.1502743

812 Aiello, A., Farzaneh, F., Candore, G., Caruso, C., Davinelli, S., Gambino, C.M.,
813 Ligotti, M.E., Zareian, N., Accardi, G., 2019. Immunosenescence and Its Hallmarks:
814 How to Oppose Aging Strategically? A Review of Potential Options for Therapeutic
815 Intervention. Front Immunol 10, 2247. https://doi.org/10.3389/fimmu.2019.02247

816 Akgün, K.M., Crothers, K., Pisani, M., 2012. Epidemiology and management of
817 common pulmonary diseases in older persons. J. Gerontol. A Biol. Sci. Med. Sci. 67,
818 276–291. https://doi.org/10.1093/gerona/glr251

819 Al-Alawi, M., Hassan, T., Chotirmall, S.H., 2014. Advances in the diagnosis and
820 management of asthma in older adults. Am. J. Med. 127, 370–378.
821 https://doi.org/10.1016/j.amjmed.2013.12.013

822 Antunes, K.H., Fachi, J.L., de Paula, R., da Silva, E.F., Pral, L.P., Dos Santos, A.Á.,
823 Dias, G.B.M., Vargas, J.E., Puga, R., Mayer, F.Q., Maito, F., Zárate-Bladés, C.R.,
824 Ajami, N.J., Sant'Ana, M.R., Candreva, T., Rodrigues, H.G., Schmiele, M., Silva
825 Clerici, M.T.P., Proença-Modena, J.L., Vieira, A.T., Mackay, C.R., Mansur, D.,
826 Caballero, M.T., Marzec, J., Li, J., Wang, X., Bell, D., Polack, F.P., Kleeberger, S.R.,
827 Stein, R.T., Vinolo, M.A.R., de Souza, A.P.D., 2019. Microbiota-derived acetate
828 protects against respiratory syncytial virus infection through a GPR43-type 1
829 interferon response. Nat Commun 10, 3273. https://doi.org/10.1038/s41467-019-
830 11152-6

831 Arnardottir, H.H., Dalli, J., Colas, R.A., Shinohara, M., Serhan, C.N., 2014. Aging
832 delays resolution of acute inflammation in mice: reprogramming the host response
833 with novel nano-proresolving medicines. J. Immunol. 193, 4235–4244.
834 https://doi.org/10.4049/jimmunol.1401313

835 Balan, E., Decottignies, A., Deldicque, L., 2018. Physical Activity and Nutrition: Two
836 Promising Strategies for Telomere Maintenance? Nutrients 10.
837 https://doi.org/10.3390/nu10121942

838 Barber, T.M., Kabisch, S., Pfeiffer, A.F.H., Weickert, M.O., 2020. The Health Benefits

of Dietary Fibre. Nutrients 12. https://doi.org/10.3390/nu12103209

Barnes, B.J., Adrover, J.M., Baxter-Stoltzfus, A., Borczuk, A., Cools-Lartigue, J., Crawford, J.M., Daßler-Plenker, J., Guerci, P., Huynh, C., Knight, J.S., Loda, M., Looney, M.R., McAllister, F., Rayes, R., Renaud, S., Rousseau, S., Salvatore, S., Schwartz, R.E., Spicer, J.D., Yost, C.C., Weber, A., Zuo, Y., Egeblad, M., 2020. Targeting potential drivers of COVID-19: Neutrophil extracellular traps. J. Exp. Med. 217. https://doi.org/10.1084/jem.20200652

Bartley, J.M., Zhou, X., Kuchel, G.A., Weinstock, G.M., Haynes, L., 2017. Impact of Age, Caloric Restriction, and Influenza Infection on Mouse Gut Microbiome: An Exploratory Study of the Role of Age-Related Microbiome Changes on Influenza Responses. Front Immunol 8, 1164. https://doi.org/10.3389/fimmu.2017.01164

Bassis, C.M., Erb-Downward, J.R., Dickson, R.P., Freeman, C.M., Schmidt, T.M., Young, V.B., Beck, J.M., Curtis, J.L., Huffnagle, G.B., 2015. Analysis of the upper respiratory tract microbiotas as the source of the lung and gastric microbiotas in healthy individuals. mBio 6, e00037. https://doi.org/10.1128/mBio.00037-15

Biagi, E., Rampelli, S., Turroni, S., Quercia, S., Candela, M., Brigidi, P., 2017. The gut microbiota of centenarians: Signatures of longevity in the gut microbiota profile. Mech. Ageing Dev. 165, 180–184. https://doi.org/10.1016/j.mad.2016.12.013

Bowdish, D.M.E., 2019. The Aging Lung: Is Lung Health Good Health for Older Adults? Chest 155, 391–400. https://doi.org/10.1016/j.chest.2018.09.003

Brinkmann, V., Zychlinsky, A., 2007. Beneficial suicide: why neutrophils die to make NETs. Nat. Rev. Microbiol. 5, 577–582. https://doi.org/10.1038/nrmicro1710

Brown, R.L., Sequeira, R.P., Clarke, T.B., 2017. The microbiota protects against respiratory infection via GM-CSF signaling. Nat Commun 8, 1512. https://doi.org/10.1038/s41467-017-01803-x

Burr, A.H.P., Bhattacharjee, A., Hand, T.W., 2020. Nutritional Modulation of the Microbiome and Immune Response. J Immunol 205, 1479–1487. https://doi.org/10.4049/jimmunol.2000419

Castle, S.C., Uyemura, K., Fulop, T., Makinodan, T., 2007. Host resistance and immune responses in advanced age. Clin. Geriatr. Med. 23, 463–479, v.

https://doi.org/10.1016/j.cger.2007.03.005

Cederholm, T., Barazzoni, R., Austin, P., Ballmer, P., Biolo, G., Bischoff, S.C., Compher, C., Correia, I., Higashiguchi, T., Holst, M., Jensen, G.L., Malone, A., Muscaritoli, M., Nyulasi, I., Pirlich, M., Rothenberg, E., Schindler, K., Schneider, S.M., de van der Schueren, M. a. E., Sieber, C., Valentini, L., Yu, J.C., Van Gossum, A., Singer, P., 2017. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr 36, 49–64. https://doi.org/10.1016/j.clnu.2016.09.004

César Machado, M.C., da Silva, F.P., 2016. Intestinal Barrier Dysfunction in Human Pathology and Aging. Curr. Pharm. Des. 22, 4645–4650. https://doi.org/10.2174/1381612822666160510125331

Chakraborty, K., Raundhal, M., Chen, B.B., Morse, C., Tyurina, Y.Y., Khare, A., Oriss, T.B., Huff, R., Lee, J.S., St Croix, C.M., Watkins, S., Mallampalli, R.K., Kagan, V.E., Ray, A., Ray, P., 2017. The mito-DAMP cardiolipin blocks IL-10 production causing persistent inflammation during bacterial pneumonia. Nat Commun 8, 13944. https://doi.org/10.1038/ncomms13944

Chen, J., Kelley, W.J., Goldstein, D.R., 2020. Role of Aging and the Immune Response to Respiratory Viral Infections: Potential Implications for COVID-19. J. Immunol. https://doi.org/10.4049/jimmunol.2000380

Chen, M.M., Palmer, J.L., Plackett, T.P., Deburghgraeve, C.R., Kovacs, E.J., 2014. Age-related differences in the neutrophil response to pulmonary pseudomonas infection. Exp. Gerontol. 54, 42–46. https://doi.org/10.1016/j.exger.2013.12.010

Cheng, C.-W., Villani, V., Buono, R., Wei, M., Kumar, S., Yilmaz, O.H., Cohen, P., Sneddon, J.B., Perin, L., Longo, V.D., 2017. Fasting-Mimicking Diet Promotes Ngn3-Driven β-Cell Regeneration to Reverse Diabetes. Cell 168, 775-788.e12. https://doi.org/10.1016/j.cell.2017.01.040

Cho, S.J., Stout-Delgado, H.W., 2020. Aging and Lung Disease. Annu. Rev. Physiol. 82, 433–459. https://doi.org/10.1146/annurev-physiol-021119-034610

Choi, J.W., Pai, S.H., 2004. Brief communication: Respiratory function is closely associated with basal metabolic rate in elderly persons. Ann. Clin. Lab. Sci. 34, 99–102.

Claesson, M.J., Cusack, S., O'Sullivan, O., Greene-Diniz, R., de Weerd, H., Flannery, E., Marchesi, J.R., Falush, D., Dinan, T., Fitzgerald, G., Stanton, C., van Sinderen, D., O'Connor, M., Harnedy, N., O'Connor, K., Henry, C., O'Mahony, D., Fitzgerald, A.P., Shanahan, F., Twomey, C., Hill, C., Ross, R.P., O'Toole, P.W., 2011. Composition, variability, and temporal stability of the intestinal microbiota of the elderly. Proc. Natl. Acad. Sci. U.S.A. 108 Suppl 1, 4586–4591. https://doi.org/10.1073/pnas.1000097107

Claesson, M.J., Jeffery, I.B., Conde, S., Power, S.E., O'Connor, E.M., Cusack, S., Harris, H.M.B., Coakley, M., Lakshminarayanan, B., O'Sullivan, O., Fitzgerald, G.F., Deane, J., O'Connor, M., Harnedy, N., O'Connor, K., O'Mahony, D., van Sinderen, D., Wallace, M., Brennan, L., Stanton, C., Marchesi, J.R., Fitzgerald, A.P., Shanahan, F., Hill, C., Ross, R.P., O'Toole, P.W., 2012. Gut microbiota composition correlates with diet and health in the elderly. Nature 488, 178–184. https://doi.org/10.1038/nature11319

Colman, R.J., Anderson, R.M., Johnson, S.C., Kastman, E.K., Kosmatka, K.J., Beasley, T.M., Allison, D.B., Cruzen, C., Simmons, H.A., Kemnitz, J.W., Weindruch, R., 2009. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science 325, 201–204. https://doi.org/10.1126/science.1173635

Colman, R.J., Beasley, T.M., Kemnitz, J.W., Johnson, S.C., Weindruch, R., Anderson, R.M., 2014. Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Nat Commun 5, 3557. https://doi.org/10.1038/ncomms4557

Cooke, K.R., Hill, G.R., Gerbitz, A., Kobzik, L., Martin, T.R., Crawford, J.M., Brewer, J.P., Ferrara, J.L., 2000. Hyporesponsiveness of donor cells to lipopolysaccharide stimulation reduces the severity of experimental idiopathic pneumonia syndrome: potential role for a gut-lung axis of inflammation. J. Immunol. 165, 6612–6619. https://doi.org/10.4049/jimmunol.165.11.6612

Corberand, J., Ngyen, F., Laharrague, P., Fontanilles, A.M., Gleyzes, B., Gyrard, E., Senegas, C., 1981. Polymorphonuclear functions and aging in humans. J Am Geriatr Soc 29, 391–397. https://doi.org/10.1111/j.1532-5415.1981.tb02376.x

Cutting, G.R., 2015. Cystic fibrosis genetics: from molecular understanding to clinical application. Nat. Rev. Genet. 16, 45–56. https://doi.org/10.1038/nrg3849

930 Cătoi, A.F., Corina, A., Katsiki, N., Vodnar, D.C., Andreicuț, A.D., Stoian, A.P., Rizzo,
931 M., Pérez-Martínez, P., 2020. Gut microbiota and aging-A focus on centenarians.
932 Biochim Biophys Acta Mol Basis Dis 1866, 165765.
933 https://doi.org/10.1016/j.bbadis.2020.165765

934 Dabrowski, A.N., Shrivastav, A., Conrad, C., Komma, K., Weigel, M., Dietert, K.,
935 Gruber, A.D., Bertrams, W., Wilhelm, J., Schmeck, B., Reppe, K., N'Guessan, P.D.,
936 Aly, S., Suttorp, N., Hain, T., Zahlten, J., 2019. Peptidoglycan Recognition Protein 4
937 Limits Bacterial Clearance and Inflammation in Lungs by Control of the Gut
938 Microbiota. Front Immunol 10, 2106. https://doi.org/10.3389/fimmu.2019.02106

939 Dalmasso, G., Cougnoux, A., Delmas, J., Darfeuille-Michaud, A., Bonnet, R., 2014.
940 The bacterial genotoxin colibactin promotes colon tumor growth by modifying the
941 tumor microenvironment. Gut Microbes 5, 675–680.
942 https://doi.org/10.4161/19490976.2014.969989

943 David, L.A., Maurice, C.F., Carmody, R.N., Gootenberg, D.B., Button, J.E., Wolfe,
944 B.E., Ling, A.V., Devlin, A.S., Varma, Y., Fischbach, M.A., Biddinger, S.B., Dutton,
945 R.J., Turnbaugh, P.J., 2014. Diet rapidly and reproducibly alters the human gut
946 microbiome. Nature 505, 559–563. https://doi.org/10.1038/nature12820

947 de Steenhuijsen Piters, W.A.A., Huijskens, E.G.W., Wyllie, A.L., Biesbroek, G., van
948 den Bergh, M.R., Veenhoven, R.H., Wang, X., Trzciński, K., Bonten, M.J., Rossen,
949 J.W.A., Sanders, E.A.M., Bogaert, D., 2016. Dysbiosis of upper respiratory tract
950 microbiota in elderly pneumonia patients. ISME J 10, 97–108.
951 https://doi.org/10.1038/ismej.2015.99

952 de Vrese, M., Schrezenmeir, J., 2008. Probiotics, prebiotics, and synbiotics. Adv.
953 Biochem. Eng. Biotechnol. 111, 1–66. https://doi.org/10.1007/10_2008_097

954 de Vrese, M., Winkler, P., Rautenberg, P., Harder, T., Noah, C., Laue, C., Ott, S.,
955 Hampe, J., Schreiber, S., Heller, K., Schrezenmeir, J., 2006. Probiotic bacteria
956 reduced duration and severity but not the incidence of common cold episodes in a
957 double blind, randomized, controlled trial. Vaccine 24, 6670–6674.
958 https://doi.org/10.1016/j.vaccine.2006.05.048

959 Deriu, E., Boxx, G.M., He, X., Pan, C., Benavidez, S.D., Cen, L., Rozengurt, N., Shi,
960 W., Cheng, G., 2016. Influenza Virus Affects Intestinal Microbiota and Secondary

961 Salmonella Infection in the Gut through Type I Interferons. PLoS Pathog. 12,
962 e1005572. https://doi.org/10.1371/journal.ppat.1005572

963 Derrien, M., van Hylckama Vlieg, J.E.T., 2015. Fate, activity, and impact of ingested
964 bacteria within the human gut microbiota. Trends Microbiol. 23, 354–366.
965 https://doi.org/10.1016/j.tim.2015.03.002

966 Derrien, M., Veiga, P., 2017. Rethinking Diet to Aid Human-Microbe Symbiosis.
967 Trends Microbiol. 25, 100–112. https://doi.org/10.1016/j.tim.2016.09.011

968 Dickson, R.P., Huffnagle, G.B., 2015. The Lung Microbiome: New Principles for
969 Respiratory Bacteriology in Health and Disease. PLoS Pathog. 11, e1004923.
970 https://doi.org/10.1371/journal.ppat.1004923

971 Dogra, S.K., Doré, J., Damak, S., 2020. Gut Microbiota Resilience: Definition, Link to
972 Health and Strategies for Intervention. Front Microbiol 11, 572921.
973 https://doi.org/10.3389/fmicb.2020.572921

974 Dumas, A., Bernard, L., Poquet, Y., Lugo-Villarino, G., Neyrolles, O., 2018. The role
975 of the lung microbiota and the gut-lung axis in respiratory infectious diseases. Cell.
976 Microbiol. 20, e12966. https://doi.org/10.1111/cmi.12966

977 Duncan, S.H., Belenguer, A., Holtrop, G., Johnstone, A.M., Flint, H.J., Lobley, G.E.,
978 2007. Reduced dietary intake of carbohydrates by obese subjects results in
979 decreased concentrations of butyrate and butyrate-producing bacteria in feces. Appl.
980 Environ. Microbiol. 73, 1073–1078. https://doi.org/10.1128/AEM.02340-06

981 Duvallet, C., Larson, K., Snapper, S., Iosim, S., Lee, A., Freer, K., May, K., Alm, E.,
982 Rosen, R., 2019. Aerodigestive sampling reveals altered microbial exchange
983 between lung, oropharyngeal, and gastric microbiomes in children with impaired
984 swallow function. PLoS One 14, e0216453.
985 https://doi.org/10.1371/journal.pone.0216453

986 Fassarella, M., Blaak, E.E., Penders, J., Nauta, A., Smidt, H., Zoetendal, E.G., 2020.
987 Gut microbiome stability and resilience: elucidating the response to perturbations in
988 order to modulate gut health. Gut. https://doi.org/10.1136/gutjnl-2020-321747

989 Fernández-Garrido, J., Ruiz-Ros, V., Buigues, C., Navarro-Martinez, R., Cauli, O.,
990 2014. Clinical features of prefrail older individuals and emerging peripheral

biomarkers: a systematic review. Arch Gerontol Geriatr 59, 7–17. https://doi.org/10.1016/j.archger.2014.02.008

Ferrucci, L., Fabbri, E., 2018. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol 15, 505–522. https://doi.org/10.1038/s41569-018-0064-2

Frasca, D., Diaz, A., Romero, M., Blomberg, B.B., 2016. The generation of memory B cells is maintained, but the antibody response is not, in the elderly after repeated influenza immunizations. Vaccine 34, 2834–2840. https://doi.org/10.1016/j.vaccine.2016.04.023

Fried, L.P., Storer, D.J., King, D.E., Lodder, F., 1991. Diagnosis of illness presentation in the elderly. J Am Geriatr Soc 39, 117–123. https://doi.org/10.1111/j.1532-5415.1991.tb01612.x

Fulop, T., Le Page, A., Fortin, C., Witkowski, J.M., Dupuis, G., Larbi, A., 2014. Cellular signaling in the aging immune system. Curr. Opin. Immunol. 29, 105–111. https://doi.org/10.1016/j.coi.2014.05.007

Galvão, I., Tavares, L.P., Corrêa, R.O., Fachi, J.L., Rocha, V.M., Rungue, M., Garcia, C.C., Cassali, G., Ferreira, C.M., Martins, F.S., Oliveira, S.C., Mackay, C.R., Teixeira, M.M., Vinolo, M.A.R., Vieira, A.T., 2018. The Metabolic Sensor GPR43 Receptor Plays a Role in the Control of Klebsiella pneumoniae Infection in the Lung. Front Immunol 9, 142. https://doi.org/10.3389/fimmu.2018.00142

Gauguet, S., D'Ortona, S., Ahnger-Pier, K., Duan, B., Surana, N.K., Lu, R., Cywes-Bentley, C., Gadjeva, M., Shan, Q., Priebe, G.P., Pier, G.B., 2015. Intestinal Microbiota of Mice Influences Resistance to Staphylococcus aureus Pneumonia. Infect. Immun. 83, 4003–4014. https://doi.org/10.1128/IAI.00037-15

GBD 2017 Diet Collaborators, 2019. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 393, 1958–1972. https://doi.org/10.1016/S0140-6736(19)30041-8

Ghosh, T.S., Rampelli, S., Jeffery, I.B., Santoro, A., Neto, M., Capri, M., Giampieri, E., Jennings, A., Candela, M., Turroni, S., Zoetendal, E.G., Hermes, G.D.A., Elodie, C., Meunier, N., Brugere, C.M., Pujos-Guillot, E., Berendsen, A.M., De Groot, L.C.P.G.M., Feskins, E.J.M., Kaluza, J., Pietruszka, B., Bielak, M.J., Comte, B.,

Maijo-Ferre, M., Nicoletti, C., De Vos, W.M., Fairweather-Tait, S., Cassidy, A., Brigidi, P., Franceschi, C., O'Toole, P.W., 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, 1218–1228. https://doi.org/10.1136/gutjnl-2019-319654

Gibson, G.R., Hutkins, R., Sanders, M.E., Prescott, S.L., Reimer, R.A., Salminen, S.J., Scott, K., Stanton, C., Swanson, K.S., Cani, P.D., Verbeke, K., Reid, G., 2017. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol 14, 491–502. https://doi.org/10.1038/nrgastro.2017.75

Giménez-Bastida, J.A., Ávila-Gálvez, M.Á., Espín, J.C., González-Sarrías, A., 2020. The gut microbiota metabolite urolithin A, but not other relevant urolithins, induces p53-dependent cellular senescence in human colon cancer cells. Food Chem. Toxicol. 139, 111260. https://doi.org/10.1016/j.fct.2020.111260

Goldstein, D.R., 2012. Role of aging on innate responses to viral infections. J. Gerontol. A Biol. Sci. Med. Sci. 67, 242–246. https://doi.org/10.1093/gerona/glr194

Grier, A., McDavid, A., Wang, B., Qiu, X., Java, J., Bandyopadhyay, S., Yang, H., Holden-Wiltse, J., Kessler, H.A., Gill, A.L., Huyck, H., Falsey, A.R., Topham, D.J., Scheible, K.M., Caserta, M.T., Pryhuber, G.S., Gill, S.R., 2018. Neonatal gut and respiratory microbiota: coordinated development through time and space. Microbiome 6, 193. https://doi.org/10.1186/s40168-018-0566-5

Groves, H.T., Cuthbertson, L., James, P., Moffatt, M.F., Cox, M.J., Tregoning, J.S., 2018. Respiratory Disease following Viral Lung Infection Alters the Murine Gut Microbiota. Front Immunol 9, 182. https://doi.org/10.3389/fimmu.2018.00182

Guan, W.-J., Liang, W.-H., Zhao, Y., Liang, H.-R., Chen, Z.-S., Li, Y.-M., Liu, X.-Q., Chen, R.-C., Tang, C.-L., Wang, T., Ou, C.-Q., Li, L., Chen, P.-Y., Sang, L., Wang, W., Li, J.-F., Li, C.-C., Ou, L.-M., Cheng, B., Xiong, S., Ni, Z.-Y., Xiang, J., Hu, Y., Liu, L., Shan, H., Lei, C.-L., Peng, Y.-X., Wei, L., Liu, Y., Hu, Y.-H., Peng, P., Wang, J.-M., Liu, J.-Y., Chen, Z., Li, G., Zheng, Z.-J., Qiu, S.-Q., Luo, J., Ye, C.-J., Zhu, S.-Y., Cheng, L.-L., Ye, F., Li, S.-Y., Zheng, J.-P., Zhang, N.-F., Zhong, N.-S., He, J.-X.,

China Medical Treatment Expert Group for COVID-19, 2020. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur. Respir. J. 55. https://doi.org/10.1183/13993003.00547-2020

Gurung, M., Li, Z., You, H., Rodrigues, R., Jump, D.B., Morgun, A., Shulzhenko, N., 2020. Role of gut microbiota in type 2 diabetes pathophysiology. EBioMedicine 51, 102590. https://doi.org/10.1016/j.ebiom.2019.11.051

Haak, B.W., Littmann, E.R., Chaubard, J.-L., Pickard, A.J., Fontana, E., Adhi, F., Gyaltshen, Y., Ling, L., Morjaria, S.M., Peled, J.U., van den Brink, M.R., Geyer, A.I., Cross, J.R., Pamer, E.G., Taur, Y., 2018. Impact of gut colonization with butyrate-producing microbiota on respiratory viral infection following allo-HCT. Blood 131, 2978–2986. https://doi.org/10.1182/blood-2018-01-828996

Hanada, S., Pirzadeh, M., Carver, K.Y., Deng, J.C., 2018. Respiratory Viral Infection-Induced Microbiome Alterations and Secondary Bacterial Pneumonia. Front Immunol 9, 2640. https://doi.org/10.3389/fimmu.2018.02640

Hao, Q., Dong, B.R., Wu, T., 2015. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database Syst Rev CD006895. https://doi.org/10.1002/14651858.CD006895.pub3

Harvie, M., Wright, C., Pegington, M., McMullan, D., Mitchell, E., Martin, B., Cutler, R.G., Evans, G., Whiteside, S., Maudsley, S., Camandola, S., Wang, R., Carlson, O.D., Egan, J.M., Mattson, M.P., Howell, A., 2013. The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women. Br. J. Nutr. 110, 1534–1547. https://doi.org/10.1017/S0007114513000792

Harvie, M.N., Pegington, M., Mattson, M.P., Frystyk, J., Dillon, B., Evans, G., Cuzick, J., Jebb, S.A., Martin, B., Cutler, R.G., Son, T.G., Maudsley, S., Carlson, O.D., Egan, J.M., Flyvbjerg, A., Howell, A., 2011. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. Int J Obes (Lond) 35, 714–727. https://doi.org/10.1038/ijo.2010.171

Haynes, L., Swain, S.L., 2006. Why aging T cells fail: implications for vaccination. Immunity 24, 663–666. https://doi.org/10.1016/j.immuni.2006.06.003

Heymsfield, S.B., Bethel, R.A., Ansley, J.D., Nixon, D.W., Rudman, D., 1979. Enteral hyperalimentation: an alternative to central venous hyperalimentation. Ann. Intern. Med. 90, 63–71. https://doi.org/10.7326/0003-4819-90-1-63

Hildebrandt, M.A., Hoffmann, C., Sherrill-Mix, S.A., Keilbaugh, S.A., Hamady, M., Chen, Y.-Y., Knight, R., Ahima, R.S., Bushman, F., Wu, G.D., 2009. High-fat diet determines the composition of the murine gut microbiome independently of obesity. Gastroenterology 137, 1716-1724.e1–2. https://doi.org/10.1053/j.gastro.2009.08.042

Ho, J.C., Chan, K.N., Hu, W.H., Lam, W.K., Zheng, L., Tipoe, G.L., Sun, J., Leung, R., Tsang, K.W., 2001. The effect of aging on nasal mucociliary clearance, beat frequency, and ultrastructure of respiratory cilia. American Journal of Respiratory and Critical Care Medicine 163, 983–988. https://doi.org/10.1164/ajrccm.163.4.9909121

Hodge, S., Hodge, G., Scicchitano, R., Reynolds, P.N., Holmes, M., 2003. Alveolar macrophages from subjects with chronic obstructive pulmonary disease are deficient in their ability to phagocytose apoptotic airway epithelial cells. Immunol. Cell Biol. 81, 289–296. https://doi.org/10.1046/j.1440-1711.2003.t01-1-01170.x

Hole, D.J., Watt, G.C., Davey-Smith, G., Hart, C.L., Gillis, C.R., Hawthorne, V.M., 1996. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. BMJ 313, 711–715; discussion 715-716. https://doi.org/10.1136/bmj.313.7059.711

Holodick, N.E., Rothstein, T.L., 2015. B cells in the aging immune system: time to consider B-1 cells. Ann. N. Y. Acad. Sci. 1362, 176–187. https://doi.org/10.1111/nyas.12825

Hu, Yongfei, Feng, Y., Wu, J., Liu, F., Zhang, Z., Hao, Y., Liang, S., Li, B., Li, J., Lv, N., Xu, Y., Zhu, B., Sun, Z., 2019. The Gut Microbiome Signatures Discriminate Healthy From Pulmonary Tuberculosis Patients. Front Cell Infect Microbiol 9, 90. https://doi.org/10.3389/fcimb.2019.00090

Hu, Yongfeng, Yang, Q., Liu, B., Dong, J., Sun, L., Zhu, Y., Su, H., Yang, J., Yang, F., Chen, X., Jin, Q., 2019. Gut microbiota associated with pulmonary tuberculosis and dysbiosis caused by anti-tuberculosis drugs. J. Infect. 78, 317–322. https://doi.org/10.1016/j.jinf.2018.08.006

Huang, S.-F., Yang, Y.-Y., Chou, K.-T., Fung, C.-P., Wang, F.-D., Su, W.-J., 2019.

1115 Systemic proinflammation after Mycobacterium tuberculosis infection was correlated
1116 to the gut microbiome in HIV-uninfected humans. Eur. J. Clin. Invest. 49, e13068.
1117 https://doi.org/10.1111/eci.13068

1118 Ichinohe, T., Pang, I.K., Kumamoto, Y., Peaper, D.R., Ho, J.H., Murray, T.S., Iwasaki,
1119 A., 2011. Microbiota regulates immune defense against respiratory tract influenza A
1120 virus infection. Proc. Natl. Acad. Sci. U.S.A. 108, 5354–5359.
1121 https://doi.org/10.1073/pnas.1019378108

1122 Inouye, S.K., Studenski, S., Tinetti, M.E., Kuchel, G.A., 2007. Geriatric syndromes:
1123 clinical, research, and policy implications of a core geriatric concept. J Am Geriatr
1124 Soc 55, 780–791. https://doi.org/10.1111/j.1532-5415.2007.01156.x

1125 Jackson, M.A., Jackson, M., Jeffery, I.B., Beaumont, M., Bell, J.T., Clark, A.G., Ley,
1126 R.E., O'Toole, P.W., Spector, T.D., Steves, C.J., 2016. Signatures of early frailty in
1127 the gut microbiota. Genome Med 8, 8. https://doi.org/10.1186/s13073-016-0262-7

1128 Janssens, J.P., Pache, J.C., Nicod, L.P., 1999. Physiological changes in respiratory
1129 function associated with ageing. The European Respiratory Journal 13, 197–205.
1130 https://doi.org/10.1034/j.1399-3003.1999.13a36.x

1131 Jeffery, I.B., Lynch, D.B., O'Toole, P.W., 2016. Composition and temporal stability of
1132 the gut microbiota in older persons. ISME J 10, 170–182.
1133 https://doi.org/10.1038/ismej.2015.88

1134 Josset, L., Engelmann, F., Haberthur, K., Kelly, S., Park, B., Kawoaka, Y., García-
1135 Sastre, A., Katze, M.G., Messaoudi, I., 2012. Increased viral loads and exacerbated
1136 innate host responses in aged macaques infected with the 2009 pandemic H1N1
1137 influenza A virus. J. Virol. 86, 11115–11127. https://doi.org/10.1128/JVI.01571-12

1138 Kagawa, Y., 1978. Impact of Westernization on the nutrition of Japanese: changes in
1139 physique, cancer, longevity and centenarians. Prev Med 7, 205–217.
1140 https://doi.org/10.1016/0091-7435(78)90246-3

1141 Kahlich, R., Kotlár, V., Skocil, V., 1975. Complex surveillance of Streptococcus
1142 pyogenes. I. Immunological surveys of anti-M antibodies and possibilities of long-
1143 term epidemiological prognosis. J Hyg Epidemiol Microbiol Immunol 19, 48–60.

1144 Kane, R.L., Shamliyan, T., Talley, K., Pacala, J., 2012. The association between

1145 geriatric syndromes and survival. J Am Geriatr Soc 60, 896–904.
1146 https://doi.org/10.1111/j.1532-5415.2012.03942.x

1147 Kang, Y., Zhang, H., Zhao, Y., Wang, Y., Wang, W., He, Y., Zhang, Wei, Zhang,
1148 Weiwei, Zhu, X., Zhou, Y., Zhang, L., Ju, Z., Shi, L., 2018. Telomere Dysfunction
1149 Disturbs Macrophage Mitochondrial Metabolism and the NLRP3 Inflammasome
1150 through the PGC-1α/TNFAIP3 Axis. Cell Rep 22, 3493–3506.
1151 https://doi.org/10.1016/j.celrep.2018.02.071

1152 Ke, Y., Li, D., Zhao, M., Liu, C., Liu, J., Zeng, A., Shi, X., Cheng, S., Pan, B., Zheng,
1153 L., Hong, H., 2018. Gut flora-dependent metabolite Trimethylamine-N-oxide
1154 accelerates endothelial cell senescence and vascular aging through oxidative stress.
1155 Free Radic. Biol. Med. 116, 88–100.
1156 https://doi.org/10.1016/j.freeradbiomed.2018.01.007

1157 Kim, M., Gu, B., Madison, M.C., Song, H.W., Norwood, K., Hill, A.A., Wu, W.-J.,
1158 Corry, D., Kheradmand, F., Diehl, G.E., 2019. Cigarette Smoke Induces Intestinal
1159 Inflammation via a Th17 Cell-Neutrophil Axis. Front Immunol 10, 75.
1160 https://doi.org/10.3389/fimmu.2019.00075

1161 Klempel, M.C., Kroeger, C.M., Bhutani, S., Trepanowski, J.F., Varady, K.A., 2012.
1162 Intermittent fasting combined with calorie restriction is effective for weight loss and
1163 cardio-protection in obese women. Nutr J 11, 98. https://doi.org/10.1186/1475-2891-
1164 11-98

1165 Kolodziejczyk, A.A., Zheng, D., Elinav, E., 2019. Diet-microbiota interactions and
1166 personalized nutrition. Nat Rev Microbiol 17, 742–753.
1167 https://doi.org/10.1038/s41579-019-0256-8

1168 Kong, F., Hua, Y., Zeng, B., Ning, R., Li, Y., Zhao, J., 2016. Gut microbiota
1169 signatures of longevity. Curr. Biol. 26, R832–R833.
1170 https://doi.org/10.1016/j.cub.2016.08.015

1171 Kovaiou, R.D., Grubeck-Loebenstein, B., 2006. Age-associated changes within CD4+
1172 T cells. Immunol. Lett. 107, 8–14. https://doi.org/10.1016/j.imlet.2006.07.006

1173 Krone, C.L., Biesbroek, G., Trzciński, K., Sanders, E.A.M., Bogaert, D., 2014.
1174 Respiratory microbiota dynamics following Streptococcus pneumoniae acquisition in
1175 young and elderly mice. Infect. Immun. 82, 1725–1731.

https://doi.org/10.1128/IAI.01290-13

Kumar, R., Sharma, A., Gupta, M., Padwad, Y., Sharma, R., 2019. Cell-Free Culture Supernatant of Probiotic Lactobacillus fermentum Protects Against H2O2-Induced Premature Senescence by Suppressing ROS-Akt-mTOR Axis in Murine Preadipocytes. Probiotics Antimicrob Proteins. https://doi.org/10.1007/s12602-019-09576-z

Lang, P.-O., Mendes, A., Socquet, J., Assir, N., Govind, S., Aspinall, R., 2012. Effectiveness of influenza vaccine in aging and older adults: comprehensive analysis of the evidence. Clin Interv Aging 7, 55–64. https://doi.org/10.2147/CIA.S25215

Lange, P., Nyboe, J., Appleyard, M., Jensen, G., Schnohr, P., 1990. Spirometric findings and mortality in never-smokers. J Clin Epidemiol 43, 867–873. https://doi.org/10.1016/0895-4356(90)90070-6

Lee, J.-J., Kim, S.-H., Lee, M.-J., Kim, B.-K., Song, W.-J., Park, H.-W., Cho, S.-H., Hong, S.-J., Chang, Y.-S., Kim, B.-S., 2019. Different upper airway microbiome and their functional genes associated with asthma in young adults and elderly individuals. Allergy 74, 709–719. https://doi.org/10.1111/all.13608

Lee, J.-Y., Jun, N.-R., Yoon, D., Shin, C., Baik, I., 2015. Association between dietary patterns in the remote past and telomere length. Eur J Clin Nutr 69, 1048–1052. https://doi.org/10.1038/ejcn.2015.58

Lee, S.Y., Mac Aogáin, M., Fam, K.D., Chia, K.L., Binte Mohamed Ali, N.A., Yap, M.M.C., Yap, E.P.H., Chotirmall, S.H., Lim, C.L., 2019. Airway microbiome composition correlates with lung function and arterial stiffness in an age-dependent manner. PLoS ONE 14, e0225636. https://doi.org/10.1371/journal.pone.0225636

Lefebvre, J.S., Masters, A.R., Hopkins, J.W., Haynes, L., 2016. Age-related impairment of humoral response to influenza is associated with changes in antigen specific T follicular helper cell responses. Sci Rep 6, 25051. https://doi.org/10.1038/srep25051

Leong, D.P., Teo, K.K., Rangarajan, S., Lopez-Jaramillo, P., Avezum, A., Orlandini, A., Seron, P., Ahmed, S.H., Rosengren, A., Kelishadi, R., Rahman, O., Swaminathan, S., Iqbal, R., Gupta, R., Lear, S.A., Oguz, A., Yusoff, K., Zatonska, K., Chifamba, J., Igumbor, E., Mohan, V., Anjana, R.M., Gu, H., Li, W., Yusuf, S.,

1207 Prospective Urban Rural Epidemiology (PURE) Study investigators, 2015. Prognostic
1208 value of grip strength: findings from the Prospective Urban Rural Epidemiology
1209 (PURE) study. Lancet 386, 266–273. https://doi.org/10.1016/S0140-6736(14)62000-6

1210 Leung, C.W., Laraia, B.A., Needham, B.L., Rehkopf, D.H., Adler, N.E., Lin, J.,
1211 Blackburn, E.H., Epel, E.S., 2014. Soda and cell aging: associations between sugar-
1212 sweetened beverage consumption and leukocyte telomere length in healthy adults
1213 from the National Health and Nutrition Examination Surveys. Am J Public Health 104,
1214 2425–2431. https://doi.org/10.2105/AJPH.2014.302151

1215 Ley, R.E., Turnbaugh, P.J., Klein, S., Gordon, J.I., 2006. Microbial ecology: human
1216 gut microbes associated with obesity. Nature 444, 1022–1023.
1217 https://doi.org/10.1038/4441022a

1218 Li, J., Zhao, F., Wang, Y., Chen, J., Tao, J., Tian, G., Wu, S., Liu, W., Cui, Q., Geng,
1219 B., Zhang, W., Weldon, R., Auguste, K., Yang, L., Liu, X., Chen, L., Yang, X., Zhu,
1220 B., Cai, J., 2017. Gut microbiota dysbiosis contributes to the development of
1221 hypertension. Microbiome 5, 14. https://doi.org/10.1186/s40168-016-0222-x

1222 Li, W., Zhu, Y., Liao, Q., Wang, Z., Wan, C., 2019. Characterization of gut microbiota
1223 in children with pulmonary tuberculosis. BMC Pediatr 19, 445.
1224 https://doi.org/10.1186/s12887-019-1782-2

1225 Li, Z., Jiao, Y., Fan, E.K., Scott, M.J., Li, Y., Li, S., Billiar, T.R., Wilson, M.A., Shi, X.,
1226 Fan, J., 2017. Aging-Impaired Filamentous Actin Polymerization Signaling Reduces
1227 Alveolar Macrophage Phagocytosis of Bacteria. J. Immunol. 199, 3176–3186.
1228 https://doi.org/10.4049/jimmunol.1700140

1229 Liu, C., Yang, L., Han, Y., Ouyang, W., Yin, W., Xu, F., 2019. Mast cells participate in
1230 regulation of lung-gut axis during Staphylococcus aureus pneumonia. Cell Prolif. 52,
1231 e12565. https://doi.org/10.1111/cpr.12565

1232 Liu, J., Liu, Y., Xiang, P., Pu, L., Xiong, H., Li, C., Zhang, M., Tan, J., Xu, Y., Song,
1233 R., Song, M., Wang, L., Zhang, W., Han, B., Yang, L., Wang, Xiaojing, Zhou, G.,
1234 Zhang, T., Li, B., Wang, Y., Chen, Z., Wang, Xianbo, 2020. Neutrophil-to-lymphocyte
1235 ratio predicts critical illness patients with 2019 coronavirus disease in the early stage.
1236 J Transl Med 18, 206. https://doi.org/10.1186/s12967-020-02374-0

1237 Liu, J.J., Crous-Bou, M., Giovannucci, E., De Vivo, I., 2016. Coffee Consumption Is

Positively Associated with Longer Leukocyte Telomere Length in the Nurses' Health Study. J. Nutr. 146, 1373–1378. https://doi.org/10.3945/jn.116.230490

López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153, 1194–1217. https://doi.org/10.1016/j.cell.2013.05.039

Lordos, E.F., Herrmann, F.R., Robine, J.-M., Balahoczky, M., Giannelli, S.V., Gold, G., Michel, J.-P., 2008. Comparative value of medical diagnosis versus physical functioning in predicting the 6-year survival of 1951 hospitalized old patients. Rejuvenation Res 11, 829–836. https://doi.org/10.1089/rej.2008.0721

Luo, M., Liu, Y., Wu, P., Luo, D.-X., Sun, Q., Zheng, H., Hu, R., Pandol, S.J., Li, Q.-F., Han, Y.-P., Zeng, Y., 2017. Alternation of Gut Microbiota in Patients with Pulmonary Tuberculosis. Front Physiol 8, 822. https://doi.org/10.3389/fphys.2017.00822

Macpherson, A.J., Uhr, T., 2004. Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria. Science 303, 1662–1665. https://doi.org/10.1126/science.1091334

Man, A.L., Gicheva, N., Nicoletti, C., 2014. The impact of ageing on the intestinal epithelial barrier and immune system. Cell Immunol 289, 112–118. https://doi.org/10.1016/j.cellimm.2014.04.001

Marco, M.L., Heeney, D., Binda, S., Cifelli, C.J., Cotter, P.D., Foligné, B., Gänzle, M., Kort, R., Pasin, G., Pihlanto, A., Smid, E.J., Hutkins, R., 2017. Health benefits of fermented foods: microbiota and beyond. Curr. Opin. Biotechnol. 44, 94–102. https://doi.org/10.1016/j.copbio.2016.11.010

Mathieu, E., Escribano-Vazquez, U., Descamps, D., Cherbuy, C., Langella, P., Riffault, S., Remot, A., Thomas, M., 2018. Paradigms of Lung Microbiota Functions in Health and Disease, Particularly, in Asthma. Front Physiol 9, 1168. https://doi.org/10.3389/fphys.2018.01168

Mathieu, E., MacPherson, C.W., Belvis, J., Mathieu, O., Robert, V., Saint-Criq, V., Langella, P., Tompkins, T.A., Thomas, M., 2020. Oral Primo-Colonizing Bacteria Modulate Inflammation and Gene Expression in Bronchial Epithelial Cells. Microorganisms 8. https://doi.org/10.3390/microorganisms8081094

Matsuzawa-Nagata, N., Takamura, T., Ando, H., Nakamura, S., Kurita, S., Misu, H., Ota, T., Yokoyama, M., Honda, M., Miyamoto, K., Kaneko, S., 2008. Increased oxidative stress precedes the onset of high-fat diet-induced insulin resistance and obesity. Metab. Clin. Exp. 57, 1071–1077. https://doi.org/10.1016/j.metabol.2008.03.010

May, A.M., Struijk, E.A., Fransen, H.P., Onland-Moret, N.C., de Wit, G.A., Boer, J.M.A., van der Schouw, Y.T., Hoekstra, J., Bueno-de-Mesquita, H.B., Peeters, P.H.M., Beulens, J.W.J., 2015. The impact of a healthy lifestyle on Disability-Adjusted Life Years: a prospective cohort study. BMC Med 13, 39. https://doi.org/10.1186/s12916-015-0287-6

McNulty, N.P., Yatsunenko, T., Hsiao, A., Faith, J.J., Muegge, B.D., Goodman, A.L., Henrissat, B., Oozeer, R., Cools-Portier, S., Gobert, G., Chervaux, C., Knights, D., Lozupone, C.A., Knight, R., Duncan, A.E., Bain, J.R., Muehlbauer, M.J., Newgard, C.B., Heath, A.C., Gordon, J.I., 2011. The Impact of a Consortium of Fermented Milk Strains on the Gut Microbiome of Gnotobiotic Mice and Monozygotic Twins. Science Translational Medicine 3, 106ra106-106ra106. https://doi.org/10.1126/scitranslmed.3002701

Meiners, S., Eickelberg, O., Königshoff, M., 2015. Hallmarks of the ageing lung. Eur. Respir. J. 45, 807–827. https://doi.org/10.1183/09031936.00186914

Metcalf, T.U., Cubas, R.A., Ghneim, K., Cartwright, M.J., Grevenynghe, J.V., Richner, J.M., Olagnier, D.P., Wilkinson, P.A., Cameron, M.J., Park, B.S., Hiscott, J.B., Diamond, M.S., Wertheimer, A.M., Nikolich-Zugich, J., Haddad, E.K., 2015. Global analyses revealed age-related alterations in innate immune responses after stimulation of pathogen recognition receptors. Aging Cell 14, 421–432. https://doi.org/10.1111/acel.12320

Milani, C., Ticinesi, A., Gerritsen, J., Nouvenne, A., Lugli, G.A., Mancabelli, L., Turroni, F., Duranti, S., Mangifesta, M., Viappiani, A., Ferrario, C., Maggio, M., Lauretani, F., De Vos, W., van Sinderen, D., Meschi, T., Ventura, M., 2016. Gut microbiota composition and Clostridium difficile infection in hospitalized elderly individuals: a metagenomic study. Sci Rep 6, 25945. https://doi.org/10.1038/srep25945

1299 Most, J., Gilmore, L.A., Smith, S.R., Han, H., Ravussin, E., Redman, L.M., 2018.
1300 Significant improvement in cardiometabolic health in healthy nonobese individuals
1301 during caloric restriction-induced weight loss and weight loss maintenance. Am. J.
1302 Physiol. Endocrinol. Metab. 314, E396–E405.
1303 https://doi.org/10.1152/ajpendo.00261.2017

1304 Muegge, B.D., Kuczynski, J., Knights, D., Clemente, J.C., González, A., Fontana, L.,
1305 Henrissat, B., Knight, R., Gordon, J.I., 2011. Diet drives convergence in gut
1306 microbiome functions across mammalian phylogeny and within humans. Science
1307 332, 970–974. https://doi.org/10.1126/science.1198719

1308 Murray, M.A., Chotirmall, S.H., 2015. The Impact of Immunosenescence on
1309 Pulmonary Disease. Mediators Inflamm. 2015, 692546.
1310 https://doi.org/10.1155/2015/692546

1311 Naito, Y., Takagi, T., Inoue, R., Kashiwagi, S., Mizushima, K., Tsuchiya, S., Itoh, Y.,
1312 Okuda, K., Tsujimoto, Y., Adachi, A., Maruyama, N., Oda, Y., Matoba, S., 2019. Gut
1313 microbiota differences in elderly subjects between rural city Kyotango and urban city
1314 Kyoto: an age-gender-matched study. J Clin Biochem Nutr 65, 125–131.
1315 https://doi.org/10.3164/jcbn.19-26

1316 Nakatani, T., Sarraj, B., Ohnishi, M., Densmore, M.J., Taguchi, T., Goetz, R.,
1317 Mohammadi, M., Lanske, B., Razzaque, M.S., 2009. In vivo genetic evidence for
1318 klotho-dependent, fibroblast growth factor 23 (Fgf23) -mediated regulation of
1319 systemic phosphate homeostasis. FASEB J. 23, 433–441.
1320 https://doi.org/10.1096/fj.08-114397

1321 Namasivayam, S., Sher, A., Glickman, M.S., Wipperman, M.F., 2018. The
1322 Microbiome and Tuberculosis: Early Evidence for Cross Talk. mBio 9.
1323 https://doi.org/10.1128/mBio.01420-18

1324 Nipper, A.J., Smithey, M.J., Shah, R.C., Canaday, D.H., Landay, A.L., 2018.
1325 Diminished antibody response to influenza vaccination is characterized by expansion
1326 of an age-associated B-cell population with low PAX5. Clin. Immunol. 193, 80–87.
1327 https://doi.org/10.1016/j.clim.2018.02.003

1328 O'Callaghan, N.J., Toden, S., Bird, A.R., Topping, D.L., Fenech, M., Conlon, M.A.,
1329 2012. Colonocyte telomere shortening is greater with dietary red meat than white

meat and is attenuated by resistant starch. Clin Nutr 31, 60–64. https://doi.org/10.1016/j.clnu.2011.09.003

O'Sullivan, Ó., Coakley, M., Lakshminarayanan, B., Claesson, M.J., Stanton, C., O'Toole, P.W., Ross, R.P., ELDERMET consortium (http://eldermet.ucc.ie), 2011. Correlation of rRNA gene amplicon pyrosequencing and bacterial culture for microbial compositional analysis of faecal samples from elderly Irish subjects. J. Appl. Microbiol. 111, 467–473. https://doi.org/10.1111/j.1365-2672.2011.05067.x

Parada Venegas, D., De la Fuente, M.K., Landskron, G., González, M.J., Quera, R., Dijkstra, G., Harmsen, H.J.M., Faber, K.N., Hermoso, M.A., 2019. Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. Front Immunol 10, 277. https://doi.org/10.3389/fimmu.2019.00277

Parrish, A.R., 2017. The impact of aging on epithelial barriers. Tissue Barriers 5, e1343172. https://doi.org/10.1080/21688370.2017.1343172

Pavanello, S., Hoxha, M., Dioni, L., Bertazzi, P.A., Snenghi, R., Nalesso, A., Ferrara, S.D., Montisci, M., Baccarelli, A., 2011. Shortened telomeres in individuals with abuse in alcohol consumption. Int. J. Cancer 129, 983–992. https://doi.org/10.1002/ijc.25999

Peng, M., Bitsko, E., Biswas, D., 2015. Functional properties of peanut fractions on the growth of probiotics and foodborne bacterial pathogens. J Food Sci 80, M635-641. https://doi.org/10.1111/1750-3841.12785

Péré-Védrenne, C., Prochazkova-Carlotti, M., Rousseau, B., He, W., Chambonnier, L., Sifré, E., Buissonnière, A., Dubus, P., Mégraud, F., Varon, C., Ménard, A., 2017. The Cytolethal Distending Toxin Subunit CdtB of Helicobacter hepaticus Promotes Senescence and Endoreplication in Xenograft Mouse Models of Hepatic and Intestinal Cell Lines. Front Cell Infect Microbiol 7, 268. https://doi.org/10.3389/fcimb.2017.00268

Pérez, L.M., Amaral, M.A., Mundstock, E., Barbé-Tuana, F.M., Guma, F.T.C.R., Jones, M.H., Machado, D.C., Sarria, E.E., Marques E Marques, M., Preto, L.T., Epifanio, M., Meinem Garbin, J.G., Mattiello, R., 2017. Effects of Diet on Telomere Length: Systematic Review and Meta-Analysis. Public Health Genomics 20, 286–

292. https://doi.org/10.1159/000486586

Poh, C.H., Navarro-Rodriguez, T., Fass, R., 2010. Review: treatment of gastroesophageal reflux disease in the elderly. Am. J. Med. 123, 496–501. https://doi.org/10.1016/j.amjmed.2009.07.036

Pugin, J., Chevrolet, J.C., 1991. [The intestine-liver-lung axis in septic syndrome]. Schweiz Med Wochenschr 121, 1538–1544.

Qin, N., Zheng, B., Yao, J., Guo, L., Zuo, J., Wu, L., Zhou, J., Liu, L., Guo, J., Ni, S., Li, A., Zhu, Y., Liang, W., Xiao, Y., Ehrlich, S.D., Li, L., 2015. Influence of H7N9 virus infection and associated treatment on human gut microbiota. Sci Rep 5, 14771. https://doi.org/10.1038/srep14771

Rampelli, S., Soverini, M., D'Amico, F., Barone, M., Tavella, T., Monti, D., Capri, M., Astolfi, A., Brigidi, P., Biagi, E., Franceschi, C., Turroni, S., Candela, M., 2020. Shotgun Metagenomics of Gut Microbiota in Humans with up to Extreme Longevity and the Increasing Role of Xenobiotic Degradation. mSystems 5. https://doi.org/10.1128/mSystems.00124-20

Rantanen, T., Volpato, S., Ferrucci, L., Heikkinen, E., Fried, L.P., Guralnik, J.M., 2003. Handgrip strength and cause-specific and total mortality in older disabled women: exploring the mechanism. J Am Geriatr Soc 51, 636–641. https://doi.org/10.1034/j.1600-0579.2003.00207.x

Rasheed, S., Woods, R.T., 2013. Malnutrition and quality of life in older people: a systematic review and meta-analysis. Ageing Res. Rev. 12, 561–566. https://doi.org/10.1016/j.arr.2012.11.003

Rea, M.C., O'Sullivan, O., Shanahan, F., O'Toole, P.W., Stanton, C., Ross, R.P., Hill, C., 2012. Clostridium difficile carriage in elderly subjects and associated changes in the intestinal microbiota. J. Clin. Microbiol. 50, 867–875. https://doi.org/10.1128/JCM.05176-11

Redman, L.M., Smith, S.R., Burton, J.H., Martin, C.K., Il'yasova, D., Ravussin, E., 2018. Metabolic Slowing and Reduced Oxidative Damage with Sustained Caloric Restriction Support the Rate of Living and Oxidative Damage Theories of Aging. Cell Metab. 27, 805-815.e4. https://doi.org/10.1016/j.cmet.2018.02.019

Rehman, T., 2012. Role of the gut microbiota in age-related chronic inflammation. Endocr Metab Immune Disord Drug Targets 12, 361–367. https://doi.org/10.2174/187153012803832620

Remot, A., Descamps, D., Noordine, M.-L., Boukadiri, A., Mathieu, E., Robert, V., Riffault, S., Lambrecht, B., Langella, P., Hammad, H., Thomas, M., 2017. Bacteria isolated from lung modulate asthma susceptibility in mice. ISME J 11, 1061–1074. https://doi.org/10.1038/ismej.2016.181

Richardson, S., Hirsch, J.S., Narasimhan, M., Crawford, J.M., McGinn, T., Davidson, K.W., and the Northwell COVID-19 Research Consortium, Barnaby, D.P., Becker, L.B., Chelico, J.D., Cohen, S.L., Cookingham, J., Coppa, K., Diefenbach, M.A., Dominello, A.J., Duer-Hefele, J., Falzon, L., Gitlin, J., Hajizadeh, N., Harvin, T.G., Hirschwerk, D.A., Kim, E.J., Kozel, Z.M., Marrast, L.M., Mogavero, J.N., Osorio, G.A., Qiu, M., Zanos, T.P., 2020. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. https://doi.org/10.1001/jama.2020.6775

Rodgers, G.P., Collins, F.S., 2020. Precision Nutrition-the Answer to “What to Eat to Stay Healthy.” JAMA. https://doi.org/10.1001/jama.2020.13601

Rosen, R., Amirault, J., Liu, H., Mitchell, P., Hu, L., Khatwa, U., Onderdonk, A., 2014. Changes in gastric and lung microflora with acid suppression: acid suppression and bacterial growth. JAMA Pediatr 168, 932–937. https://doi.org/10.1001/jamapediatrics.2014.696

Samuelson, D.R., Charles, T.P., de la Rua, N.M., Taylor, C.M., Blanchard, E.E., Luo, M., Shellito, J.E., Welsh, D.A., 2016. Analysis of the intestinal microbial community and inferred functional capacities during the host response to Pneumocystis pneumonia. Exp. Lung Res. 42, 425–439. https://doi.org/10.1080/01902148.2016.1258442

Santoro, A., Ostan, R., Candela, M., Biagi, E., Brigidi, P., Capri, M., Franceschi, C., 2018. Gut microbiota changes in the extreme decades of human life: a focus on centenarians. Cell. Mol. Life Sci. 75, 129–148. https://doi.org/10.1007/s00018-017-2674-y

Schuijt, T.J., Lankelma, J.M., Scicluna, B.P., de Sousa e Melo, F., Roelofs, J.J.T.H.,

de Boer, J.D., Hoogendijk, A.J., de Beer, R., de Vos, A., Belzer, C., de Vos, W.M., van der Poll, T., Wiersinga, W.J., 2016. The gut microbiota plays a protective role in the host defence against pneumococcal pneumonia. Gut 65, 575–583. https://doi.org/10.1136/gutjnl-2015-309728

Segata, N., Haake, S.K., Mannon, P., Lemon, K.P., Waldron, L., Gevers, D., Huttenhower, C., Izard, J., 2012. Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. Genome Biol. 13, R42. https://doi.org/10.1186/gb-2012-13-6-r42

Sencio, V., Barthelemy, A., Tavares, L.P., Machado, M.G., Soulard, D., Cuinat, C., Queiroz-Junior, C.M., Noordine, M.-L., Salomé-Desnoulez, S., Deryuter, L., Foligné, B., Wahl, C., Frisch, B., Vieira, A.T., Paget, C., Milligan, G., Ulven, T., Wolowczuk, I., Faveeuw, C., Le Goffic, R., Thomas, M., Ferreira, S., Teixeira, M.M., Trottein, F., 2020. Gut Dysbiosis during Influenza Contributes to Pulmonary Pneumococcal Superinfection through Altered Short-Chain Fatty Acid Production. Cell Rep 30, 2934-2947.e6. https://doi.org/10.1016/j.celrep.2020.02.013

Shaw, A.C., Panda, A., Joshi, S.R., Qian, F., Allore, H.G., Montgomery, R.R., 2011. Dysregulation of human Toll-like receptor function in aging. Ageing Res. Rev. 10, 346–353. https://doi.org/10.1016/j.arr.2010.10.007

Simpson, C.F., Punjabi, N.M., Wolfenden, L., Shardell, M., Shade, D.M., Fried, L.P., 2005. Relationship between lung function and physical performance in disabled older women. J. Gerontol. A Biol. Sci. Med. Sci. 60, 350–354. https://doi.org/10.1093/gerona/60.3.350

Smith, D.L., Mattison, J.A., Desmond, R.A., Gardner, J.P., Kimura, M., Roth, G.S., Ingram, D.K., Allison, D.B., Aviv, A., 2011. Telomere dynamics in rhesus monkeys: no apparent effect of caloric restriction. J. Gerontol. A Biol. Sci. Med. Sci. 66, 1163–1168. https://doi.org/10.1093/gerona/glr136

Sone, H., Kagawa, Y., 2005. Pancreatic beta cell senescence contributes to the pathogenesis of type 2 diabetes in high-fat diet-induced diabetic mice. Diabetologia 48, 58–67. https://doi.org/10.1007/s00125-004-1605-2

Stearns, J.C., Davidson, C.J., McKeon, S., Whelan, F.J., Fontes, M.E., Schryvers, A.B., Bowdish, D.M.E., Kellner, J.D., Surette, M.G., 2015. Culture and molecular-

based profiles show shifts in bacterial communities of the upper respiratory tract that occur with age. ISME J 9, 1246–1259. https://doi.org/10.1038/ismej.2014.250

Stekovic, S., Hofer, S.J., Tripolt, N., Aon, M.A., Royer, P., Pein, L., Stadler, J.T., Pendl, T., Prietl, B., Url, J., Schroeder, S., Tadic, J., Eisenberg, T., Magnes, C., Stumpe, M., Zuegner, E., Bordag, N., Riedl, R., Schmidt, A., Kolesnik, E., Verheyen, N., Springer, A., Madl, T., Sinner, F., de Cabo, R., Kroemer, G., Obermayer-Pietsch, B., Dengjel, J., Sourij, H., Pieber, T.R., Madeo, F., 2019. Alternate Day Fasting Improves Physiological and Molecular Markers of Aging in Healthy, Non-obese Humans. Cell Metab. 30, 462-476.e6. https://doi.org/10.1016/j.cmet.2019.07.016

Stout-Delgado, H.W., Vaughan, S.E., Shirali, A.C., Jaramillo, R.J., Harrod, K.S., 2012. Impaired NLRP3 inflammasome function in elderly mice during influenza infection is rescued by treatment with nigericin. J. Immunol. 188, 2815–2824. https://doi.org/10.4049/jimmunol.1103051

Struijk, E.A., Beulens, J.W.J., May, A.M., Fransen, H.P., Boer, J.M.A., de Wit, G.A., Onland-Moret, N.C., van der Schouw, Y.T., Hoekstra, J., Bueno-de-Mesquita, H.B., Peeters, P.H.M., 2014. Dietary patterns in relation to disease burden expressed in Disability-Adjusted Life Years. Am. J. Clin. Nutr. 100, 1158–1165. https://doi.org/10.3945/ajcn.113.082032

Suzuki, M., Betsuyaku, T., Ito, Y., Nagai, K., Nasuhara, Y., Kaga, K., Kondo, S., Nishimura, M., 2008. Down-regulated NF-E2-related factor 2 in pulmonary macrophages of aged smokers and patients with chronic obstructive pulmonary disease. Am. J. Respir. Cell Mol. Biol. 39, 673–682. https://doi.org/10.1165/rcmb.2007-0424OC

Suzuki, M., Wilcox, B.J., Wilcox, C.D., 2001. Implications from and for food cultures for cardiovascular disease: longevity. Asia Pac J Clin Nutr 10, 165–171. https://doi.org/10.1111/j.1440-6047.2001.00219.x

Sze, M.A., Tsuruta, M., Yang, S.-W.J., Oh, Y., Man, S.F.P., Hogg, J.C., Sin, D.D., 2014. Changes in the bacterial microbiota in gut, blood, and lungs following acute LPS instillation into mice lungs. PLoS ONE 9, e111228. https://doi.org/10.1371/journal.pone.0111228

Tamang, J.P., Shin, D.-H., Jung, S.-J., Chae, S.-W., 2016. Functional Properties of

Microorganisms in Fermented Foods. Front. Microbiol. 7. https://doi.org/10.3389/fmicb.2016.00578

Tankersley, C.G., Shank, J.A., Flanders, S.E., Soutiere, S.E., Rabold, R., Mitzner, W., Wagner, E.M., 2003. Changes in lung permeability and lung mechanics accompany homeostatic instability in senescent mice. J. Appl. Physiol. 95, 1681–1687. https://doi.org/10.1152/japplphysiol.00190.2003

Tanner, M.R., Beeton, C., 2018. Differences in ion channel phenotype and function between humans and animal models. Front Biosci (Landmark Ed) 23, 43–64. https://doi.org/10.2741/4581

Tappenden, K.A., Quatrara, B., Parkhurst, M.L., Malone, A.M., Fanjiang, G., Ziegler, T.R., 2013. Critical role of nutrition in improving quality of care: an interdisciplinary call to action to address adult hospital malnutrition. JPEN J Parenter Enteral Nutr 37, 482–497. https://doi.org/10.1177/0148607113484066

Taylor, B.C., Lejzerowicz, F., Poirel, M., Shaffer, J.P., Jiang, L., Aksenov, A., Litwin, N., Humphrey, G., Martino, C., Miller-Montgomery, S., Dorrestein, P.C., Veiga, P., Song, S.J., McDonald, D., Derrien, M., Knight, R., 2020. Consumption of Fermented Foods Is Associated with Systematic Differences in the Gut Microbiome and Metabolome. mSystems 5. https://doi.org/10.1128/mSystems.00901-19

Thevaranjan, N., Puchta, A., Schulz, C., Naidoo, A., Szamosi, J.C., Verschoor, C.P., Loukov, D., Schenck, L.P., Jury, J., Foley, K.P., Schertzer, J.D., Larché, M.J., Davidson, D.J., Verdú, E.F., Surette, M.G., Bowdish, D.M.E., 2017. Age-Associated Microbial Dysbiosis Promotes Intestinal Permeability, Systemic Inflammation, and Macrophage Dysfunction. Cell Host Microbe 21, 455-466.e4. https://doi.org/10.1016/j.chom.2017.03.002

Thevaranjan, N., Whelan, F.J., Puchta, A., Ashu, E., Rossi, L., Surette, M.G., Bowdish, D.M.E., 2016. Streptococcus pneumoniae Colonization Disrupts the Microbial Community within the Upper Respiratory Tract of Aging Mice. Infect. Immun. 84, 906–916. https://doi.org/10.1128/IAI.01275-15

Toapanta, F.R., Ross, T.M., 2009. Impaired immune responses in the lungs of aged mice following influenza infection. Respir. Res. 10, 112. https://doi.org/10.1186/1465-9921-10-112

Trompette, A., Gollwitzer, E.S., Pattaroni, C., Lopez-Mejia, I.C., Riva, E., Pernot, J., Ubags, N., Fajas, L., Nicod, L.P., Marsland, B.J., 2018. Dietary Fiber Confers Protection against Flu by Shaping Ly6c- Patrolling Monocyte Hematopoiesis and CD8+ T Cell Metabolism. Immunity 48, 992-1005.e8. https://doi.org/10.1016/j.immuni.2018.04.022

Trompette, A., Gollwitzer, E.S., Yadava, K., Sichelstiel, A.K., Sprenger, N., Ngom-Bru, C., Blanchard, C., Junt, T., Nicod, L.P., Harris, N.L., Marsland, B.J., 2014. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nat. Med. 20, 159–166. https://doi.org/10.1038/nm.3444

Trottein, F., Sokol, H., 2020. Potential Causes and Consequences of Gastrointestinal Disorders during a SARS-CoV-2 Infection. Cell Reports 107915. https://doi.org/10.1016/j.celrep.2020.107915

Tucker, L.A., 2018. Dietary Fiber and Telomere Length in 5674 U.S. Adults: An NHANES Study of Biological Aging. Nutrients 10. https://doi.org/10.3390/nu10040400

Valkenburg, S.A., Venturi, V., Dang, T.H.Y., Bird, N.L., Doherty, P.C., Turner, S.J., Davenport, M.P., Kedzierska, K., 2012. Early priming minimizes the age-related immune compromise of $CD8^+$ T cell diversity and function. PLoS Pathog. 8, e1002544. https://doi.org/10.1371/journal.ppat.1002544

Vandeputte, D., Joossens, M., 2020. Effects of Low and High FODMAP Diets on Human Gastrointestinal Microbiota Composition in Adults with Intestinal Diseases: A Systematic Review. Microorganisms 8. https://doi.org/10.3390/microorganisms8111638

Varady, K.A., Dam, V.T., Klempel, M.C., Horne, M., Cruz, R., Kroeger, C.M., Santosa, S., 2015. Effects of weight loss via high fat vs. low fat alternate day fasting diets on free fatty acid profiles. Sci Rep 5, 7561. https://doi.org/10.1038/srep07561

Vareille-Delarbre, M., Miquel, S., Garcin, S., Bertran, T., Balestrino, D., Evrard, B., Forestier, C., 2019. Immunomodulatory Effects of Lactobacillus plantarum on Inflammatory Response Induced by Klebsiella pneumoniae. Infect. Immun. 87. https://doi.org/10.1128/IAI.00570-19

Vaughan, A., Frazer, Z.A., Hansbro, P.M., Yang, I.A., 2019. COPD and the gut-lung

axis: the therapeutic potential of fibre. J Thorac Dis 11, S2173–S2180. https://doi.org/10.21037/jtd.2019.10.40

Vial, G., Dubouchaud, H., Couturier, K., Cottet-Rousselle, C., Taleux, N., Athias, A., Galinier, A., Casteilla, L., Leverve, X.M., 2011. Effects of a high-fat diet on energy metabolism and ROS production in rat liver. J. Hepatol. 54, 348–356. https://doi.org/10.1016/j.jhep.2010.06.044

Volkova, M., Zhang, Y., Shaw, A.C., Lee, P.J., 2012. The role of Toll-like receptors in age-associated lung diseases. J. Gerontol. A Biol. Sci. Med. Sci. 67, 247–253. https://doi.org/10.1093/gerona/glr226

Vonaesch, P., Morien, E., Andrianonimiadana, L., Sanke, H., Mbecko, J.-R., Huus, K.E., Naharimanananirina, T., Gondje, B.P., Nigatoloum, S.N., Vondo, S.S., Kaleb Kandou, J.E., Randremanana, R., Rakotondrainipiana, M., Mazel, F., Djorie, S.G., Gody, J.-C., Finlay, B.B., Rubbo, P.-A., Wegener Parfrey, L., Collard, J.-M., Sansonetti, P.J., Afribiota Investigators, 2018. Stunted childhood growth is associated with decompartmentalization of the gastrointestinal tract and overgrowth of oropharyngeal taxa. Proc. Natl. Acad. Sci. U.S.A. 115, E8489–E8498. https://doi.org/10.1073/pnas.1806573115

Walker, A.W., Ince, J., Duncan, S.H., Webster, L.M., Holtrop, G., Ze, X., Brown, D., Stares, M.D., Scott, P., Bergerat, A., Louis, P., McIntosh, F., Johnstone, A.M., Lobley, G.E., Parkhill, J., Flint, H.J., 2011. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. ISME J 5, 220–230. https://doi.org/10.1038/ismej.2010.118

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong, Y., Zhao, Y., Li, Y., Wang, X., Peng, Z., 2020. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. https://doi.org/10.1001/jama.2020.1585

Wang, F., Nie, J., Wang, H., Zhao, Q., Xiong, Y., Deng, L., Song, S., Ma, Z., Mo, P., Zhang, Y., 2020. Characteristics of Peripheral Lymphocyte Subset Alteration in COVID-19 Pneumonia. J. Infect. Dis. 221, 1762–1769. https://doi.org/10.1093/infdis/jiaa150

Wang, J., Li, F., Wei, H., Lian, Z.-X., Sun, R., Tian, Z., 2014. Respiratory influenza

virus infection induces intestinal immune injury via microbiota-mediated Th17 cell-dependent inflammation. J. Exp. Med. 211, 2397–2410. https://doi.org/10.1084/jem.20140625

Wang, N., Li, R., Lin, H., Fu, C., Wang, X., Zhang, Y., Su, M., Huang, P., Qian, J., Jiang, F., Wang, H., Jiang, L., Yu, X., Liu, J., Chen, Y., Jiang, Q., 2019. Enriched taxa were found among the gut microbiota of centenarians in East China. PLoS ONE 14, e0222763. https://doi.org/10.1371/journal.pone.0222763

Wang, S.-Y., Wang, W.-J., Liu, J.-Q., Song, Y.-H., Li, P., Sun, X.-F., Cai, G.-Y., Chen, X.-M., 2019. Methionine restriction delays senescence and suppresses the senescence-associated secretory phenotype in the kidney through endogenous hydrogen sulfide. Cell Cycle 18, 1573–1587. https://doi.org/10.1080/15384101.2019.1618124

Wang, Y., Li, X., Ge, T., Xiao, Y., Liao, Y., Cui, Y., Zhang, Y., Ho, W., Yu, G., Zhang, T., 2016. Probiotics for prevention and treatment of respiratory tract infections in children: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 95, e4509. https://doi.org/10.1097/MD.0000000000004509

Wansleeben, C., Bowie, E., Hotten, D.F., Yu, Y.-R.A., Hogan, B.L.M., 2014. Age-related changes in the cellular composition and epithelial organization of the mouse trachea. PloS One 9, e93496. https://doi.org/10.1371/journal.pone.0093496

Watson, H., Mitra, S., Croden, F.C., Taylor, M., Wood, H.M., Perry, S.L., Spencer, J.A., Quirke, P., Toogood, G.J., Lawton, C.L., Dye, L., Loadman, P.M., Hull, M.A., 2018. A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota. Gut 67, 1974–1983. https://doi.org/10.1136/gutjnl-2017-314968

Weindruch, R., Walford, R.L., Fligiel, S., Guthrie, D., 1986. The retardation of aging in mice by dietary restriction: longevity, cancer, immunity and lifetime energy intake. J. Nutr. 116, 641–654. https://doi.org/10.1093/jn/116.4.641

Weiss, E.P., Racette, S.B., Villareal, D.T., Fontana, L., Steger-May, K., Schechtman, K.B., Klein, S., Holloszy, J.O., Washington University School of Medicine CALERIE Group, 2006. Improvements in glucose tolerance and insulin action induced by increasing energy expenditure or decreasing energy intake: a randomized controlled

trial. Am. J. Clin. Nutr. 84, 1033–1042. https://doi.org/10.1093/ajcn/84.5.1033

Weiss, S.T., Segal, M.R., Sparrow, D., Wager, C., 1995. Relation of FEV1 and peripheral blood leukocyte count to total mortality. The Normative Aging Study. Am. J. Epidemiol. 142, 493–498; discussion 499-503. https://doi.org/10.1093/oxfordjournals.aje.a117665

Whelan, F.J., Verschoor, C.P., Stearns, J.C., Rossi, L., Luinstra, K., Loeb, M., Smieja, M., Johnstone, J., Surette, M.G., Bowdish, D.M.E., 2014. The loss of topography in the microbial communities of the upper respiratory tract in the elderly. Ann Am Thorac Soc 11, 513–521. https://doi.org/10.1513/AnnalsATS.201310-351OC

Winglee, K., Eloe-Fadrosh, E., Gupta, S., Guo, H., Fraser, C., Bishai, W., 2014. Aerosol Mycobacterium tuberculosis infection causes rapid loss of diversity in gut microbiota. PLoS ONE 9, e97048. https://doi.org/10.1371/journal.pone.0097048

Wong, C.K., Smith, C.A., Sakamoto, K., Kaminski, N., Koff, J.L., Goldstein, D.R., 2017. Aging Impairs Alveolar Macrophage Phagocytosis and Increases Influenza-Induced Mortality in Mice. J. Immunol. 199, 1060–1068. https://doi.org/10.4049/jimmunol.1700397

Wu, G.D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y.-Y., Keilbaugh, S.A., Bewtra, M., Knights, D., Walters, W.A., Knight, R., Sinha, R., Gilroy, E., Gupta, K., Baldassano, R., Nessel, L., Li, H., Bushman, F.D., Lewis, J.D., 2011. Linking long-term dietary patterns with gut microbial enterotypes. Science 334, 105–108. https://doi.org/10.1126/science.1208344

Wu, L., Zeng, T., Deligios, M., Milanesi, L., Langille, M.G.I., Zinellu, A., Rubino, S., Carru, C., Kelvin, D.J., 2020. Age-Related Variation of Bacterial and Fungal Communities in Different Body Habitats across the Young, Elderly, and Centenarians in Sardinia. mSphere 5. https://doi.org/10.1128/mSphere.00558-19

Yang, R., Chen, J., Zhang, J., Qin, R., Wang, R., Qiu, Y., Mao, Z., Goltzman, D., Miao, D., 2020. 1,25-Dihydroxyvitamin D protects against age-related osteoporosis by a novel VDR-Ezh2-p16 signal axis. Aging Cell 19, e13095. https://doi.org/10.1111/acel.13095

Yildiz, S., Mazel-Sanchez, B., Kandasamy, M., Manicassamy, B., Schmolke, M., 2018. Influenza A virus infection impacts systemic microbiota dynamics and causes

quantitative enteric dysbiosis. Microbiome 6, 9. https://doi.org/10.1186/s40168-017-0386-z

Yu, B., Dai, C., Chen, J., Deng, L., Wu, X., Wu, S., Zhao, C., Jiang, Z., Chen, X., 2015. Dysbiosis of gut microbiota induced the disorder of helper T cells in influenza virus-infected mice. Hum Vaccin Immunother 11, 1140–1146. https://doi.org/10.1080/21645515.2015.1009805

Zacca, E.R., Crespo, M.I., Acland, R.P., Roselli, E., Núñez, N.G., Maccioni, M., Maletto, B.A., Pistoresi-Palencia, M.C., Morón, G., 2015. Aging Impairs the Ability of Conventional Dendritic Cells to Cross-Prime CD8+ T Cells upon Stimulation with a TLR7 Ligand. PLoS ONE 10, e0140672. https://doi.org/10.1371/journal.pone.0140672

Zhang, C., Wang, X.-M., Li, S.-R., Twelkmeyer, T., Wang, W.-H., Zhang, S.-Y., Wang, S.-F., Chen, J.-Z., Jin, X., Wu, Y.-Z., Chen, X.-W., Wang, S.-D., Niu, J.-Q., Chen, H.-R., Tang, H., 2019. NKG2A is a NK cell exhaustion checkpoint for HCV persistence. Nat Commun 10, 1507. https://doi.org/10.1038/s41467-019-09212-y

Zhang, Y., Wang, Y., Gilmore, X., Xu, K., Wyde, P.R., Mbawuike, I.N., 2002. An aged mouse model for RSV infection and diminished CD8(+) CTL responses. Exp. Biol. Med. (Maywood) 227, 133–140. https://doi.org/10.1177/153537020222700208

Zhao, Jincun, Zhao, Jingxian, Legge, K., Perlman, S., 2011. Age-related increases in PGD(2) expression impair respiratory DC migration, resulting in diminished T cell responses upon respiratory virus infection in mice. J. Clin. Invest. 121, 4921–4930. https://doi.org/10.1172/JCI59777

Zheng, M., Gao, Y., Wang, G., Song, G., Liu, S., Sun, D., Xu, Y., Tian, Z., 2020. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell. Mol. Immunol. 17, 533–535. https://doi.org/10.1038/s41423-020-0402-2

Zhu, H., Pace, F., Sangaletti, O., Bianchi Porro, G., 1993. Features of symptomatic gastroesophageal reflux in elderly patients. Scand. J. Gastroenterol. 28, 235–238. https://doi.org/10.3109/00365529309096078

Zhu, Y., Lin, X., Zhao, F., Shi, X., Li, H., Li, Y., Zhu, W., Xu, X., Li, C., Zhou, G., 2015. Meat, dairy and plant proteins alter bacterial composition of rat gut bacteria. Sci Rep 5, 15220. https://doi.org/10.1038/srep15220

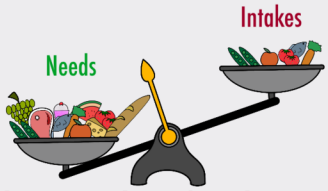
FIGURE LEGENDS

Figure 1: Microbiota is a central element connecting malnutrition and declining physiological functions in the elderly. The decline in many physiological functions, occurring at an advanced age, are associated with changes in the microbiota structure and function in the gut and other organs. These aspects are affected by type and composition of food intake and diets.

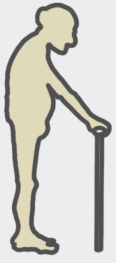
Figure 2: Hallmarks of the ageing lung and key cellular players involved in senescence.

Figure 3: Continuum and basis for the communication pathways between the gut and lung microbiota. The oral and nasal cavities are the major points of entry for microorganisms to colonise both the gastrointestinal and the respiratory tracts. In addition, transport of metabolites and immune cells through the blood and lymph circulatory systems allows for signal transduction between the two tissues.

Figure 4: The slippery slope of malnutrition in the elderly. Malnutrition in the elderly leads to a sequence of reversible and irreversible pathophysiological changes leading to the degradation of the general state of the individual. One of the early signs of a degrading health is lung infection. We propose that targeting malnutrition, and more specifically gut microbiota, using probiotics containing foods, would help reverse this chain of events, thus preventing further health degradation.



Inadequate diet / malnutrition



Gut/Lung Microbiota

Dysbiosis
Changes in composition, activity and topography

Declining physiological functions

Cognitive

Memory deterioration
Dementia
Memory loss

Sensory

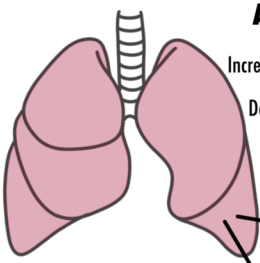
Taste, smell and appetite deterioration

Immunity

Inflamm-ageing
Increased frequency of infections
Immune exhaustion

Musculoskeletal

Loss in muscle mass
Loss in strength
Increased frailty and risk of fracture



Aged lung

Increased stiffness

Decreased mucociliary clearance

Loss in microbiota topography

Enlarged alveoli

Age-related lung diseases

COPD

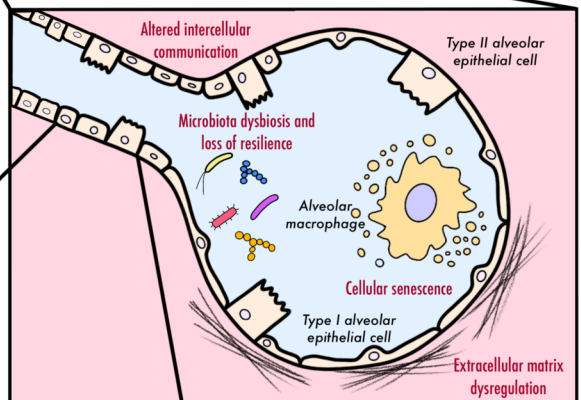
Iodiopathic pulmonary fibrosis

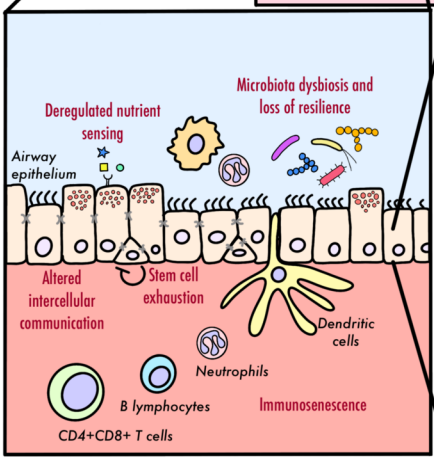
Lung cancer

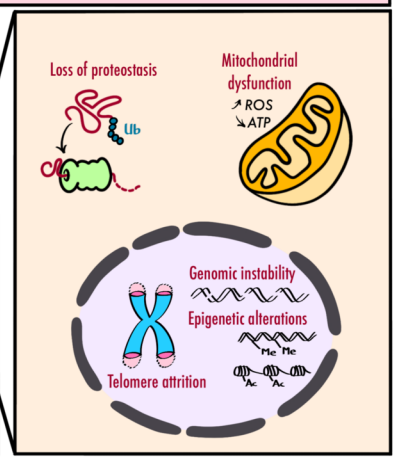
Asthma

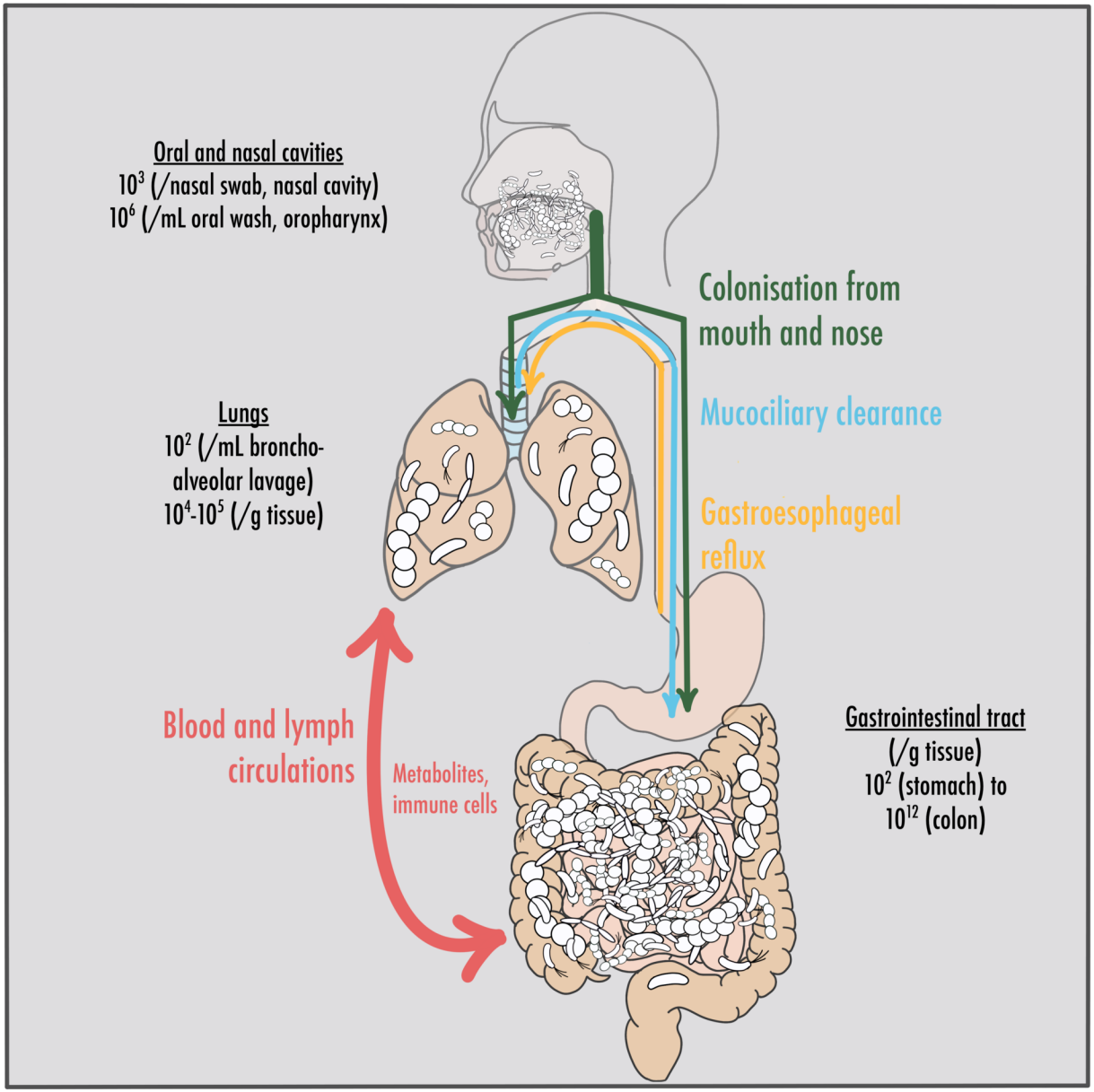
Community acquired pneumonia

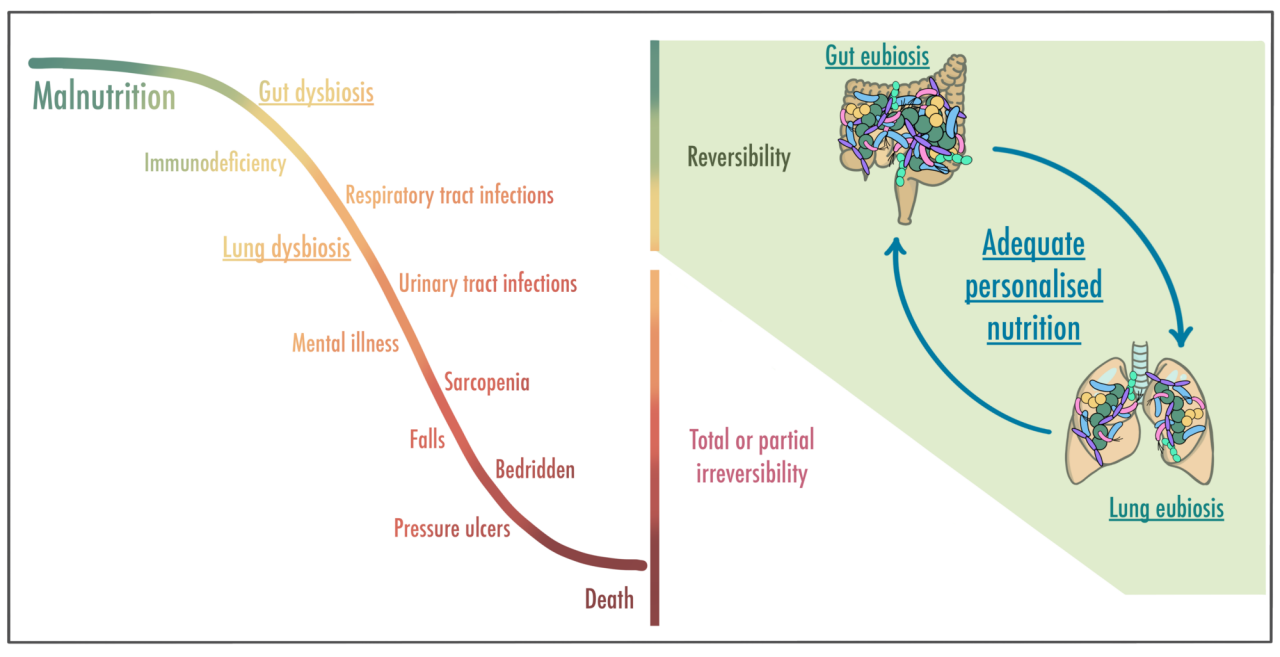
Hallmarks of the ageing lung








Oral and nasal cavities
10^3 (/nasal swab, nasal cavity)
10^6 (/mL oral wash, oropharynx)
Colonisation from mouth and nose
Mucociliary clearance
Gastroesophageal reflux
Lungs
10^2 (/mL broncho-alveolar lavage)
10^4-10^5 (/g tissue)
Blood and lymph circulations
Metabolites, immune cells
Gastrointestinal tract
(/g tissue)
10^2 (stomach) to 10^{12} (colon)


Malnutrition
Gut dysbiosis
Immunodeficiency
Respiratory tract infections
Lung dysbiosis
Urinary tract infections
Mental illness
Sarcopenia
Falls
Bedridden
Pressure ulcers
Death
Gut eubiosis
Reversibility
Adequate personalised nutrition
Total or partial irreversibility
Lung eubiosis