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► To cite this version:

Vinciane Saint-Criq, Geanncarlo Lugo-Villarino, Muriel Thomas. Dysbiosis, malnutrition and enhanced gut-lung axis contribute to age-related respiratory diseases. *Ageing Research Reviews - ARR*, 2021, 66, pp.101235. 10.1016/j.arr.2020.101235 . hal-03129383

HAL Id: hal-03129383

<https://hal.inrae.fr/hal-03129383v1>

Submitted on 2 Jan 2023

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1 DYSBIOSIS, MALNUTRITION AND ENHANCED GUT-LUNG AXIS CONTRIBUTE TO 2 AGE-RELATED RESPIRATORY DISEASES

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18 19 HIGHLIGHTS

- 20
- 21 • Older people are often malnourished and susceptible to develop lung diseases.
 - 22 • Ageing is associated with dysbiotic microbiota and alteration of the gut-lung axis.
 - 23 • Nutrition is an accessible lever affecting microbiota and ageing of the lung.
 - 24 • Gut and lung microbiota represent key players in the maintenance of healthy lungs.
 - 25 • Gut and lung microbiota are potential targets against ageing-related lung disease.
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31 **ABSTRACT**

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

46

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

49

50

51 **INTRODUCTION.**

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

58 Ageing reflects all the changes taking place over the course of life. Its process has a high
59 inter-individual variability with respect to its rate and affected organs, and is characterized by
60 a decrease in physical capacity, an increased vulnerability to environmental challenges, and
61 a growing risk of disease and death. Physiologically, loss in muscle mass, decline in strength
62 (Leong et al., 2015; Rantanen et al., 2003), and increased risk of fracture, are commonly
63 associated with ageing. Impairments in sensory functions, increased frequency of infections,
64 falls, pressure ulcers and deterioration in cognitive functions (Fernández-Garrido et al., 2014;
65 Fried et al., 1991; Inouye et al., 2007), are negatively correlated with survival (Kane et al.,
66 2012; Lordos et al., 2008). Particularly, the elderly population is at risk of developing lung
67 infections. The prevalence of other pulmonary diseases, (*e.g.* tuberculosis, chronic
68 obstructive pulmonary diseases, asthma), increases with age and contributes to morbidity
69 and mortality in older individuals. At a cellular level, ageing is associated with
70 immunosenescence (Lang et al., 2012) and with chronic low-level inflammation, known as
71 inflamm-ageing (Ferrucci and Fabbri, 2018).

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

78 impaired respiratory function and death (Rasheed and Woods, 2013; Tappenden et al.,
79 2013). Interestingly, an early study by Heymsfield *et al.* showed an association between
80 malnutrition and the apparition of further pathologies, including bronchopneumonia
81 (Heymsfield et al., 1979). Thus, because nutrition is one of the most accessible modifiable
82 factors, it can be considered as a lever of action to promote healthy ageing in older people
83 (Rodgers and Collins, 2020).

84 Many clinical issues observed in ageing individuals are associated with changes in the
85 microbiota composition and functionality in the gut and other organs (Claesson et al., 2012,
86 2011; Jackson et al., 2016; Jeffery et al., 2016; O'Sullivan et al., 2011). Although there is a
87 very high inter-individual variability, multiple studies have shown that the diversity of gut
88 microbiota and genera such as *Bifidobacteria* and *Lactobacilli* are reduced in older
89 individuals, whereas certain opportunists (*e.g. Clostridioides difficile*) are increased
90 (Claesson et al., 2011; Milani et al., 2016; Rea et al., 2012). Moreover, specific microbial
91 profiles have been identified as longevity signatures in centenarians (Biagi et al., 2017; Cătoi
92 et al., 2020; Kong et al., 2016; Naito et al., 2019; Rampelli et al., 2020; Santoro et al., 2018;
93 N. Wang et al., 2019; Wu et al., 2020). In the lungs, due to the invasiveness of the
94 procedure, no study has been performed on lower respiratory tract microbiota and only a few
95 studies have described the composition of the upper respiratory tract (URT) microbiota in the
96 elderly (de Steenhuijsen Piters et al., 2016; J.-J. Lee et al., 2019; Stearns et al., 2015;
97 Whelan et al., 2014). It is not fully understood how the microbiota impacts ageing processes,
98 but it is likely that dysbiosis plays a central role in the progression of ageing-related disorders
99 and that restoration of eubiosis would promote healthy ageing (Figure 1).

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

105 1. AGEING IN THE LUNGS

106 1.1. *The ageing lung and the most prevalent age-related pulmonary diseases*

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

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

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

135 As a consequence of the natural accumulation of age-related physiological changes in
136 addition to exposure to toxic environmental factors, this organ becomes susceptible to
137 chronic disorders such as *Chronic Obstructive Pulmonary Disease (COPD)*, *Idiopathic*
138 *Pulmonary Fibrosis (IPF)*, *Lung cancer and asthma*, and infectious diseases like *Community*
139 *Acquired Pneumonia (CAP)*. In particular, the age-associated alterations of the immune
140 system, called immunosenescence and discussed in the next section, are thought to be a
141 key driver of asthma exacerbation in the elderly (Cho and Stout-Delgado, 2020; Z. Li et al.,
142 2017; Metcalf et al., 2015; Shaw et al., 2011). Similarly, immunosenescence is thought to be
143 the main culprit for predisposing the ageing lung to immunopathology in response to
144 infectious stimuli (Chen et al., 2020; Cho and Stout-Delgado, 2020; Goldstein, 2012) and
145 consequently, the ageing lung is more predisposed to secondary bacterial infections
146 consecutive to viral pneumonia (Akgün et al., 2012; Castle et al., 2007; Chen et al., 2020;
147 Cho and Stout-Delgado, 2020; Goldstein, 2012). According to the WHO-Europe, older adults
148 are at a significant increased risk of severe disease from SARS-CoV-2 infection; over 95% of
149 the reported fatalities occurred in those individuals over 60 years old and with comorbidities.
150 Recent data indicate clear effects on the immune system, which may be worsen in older
151 individuals (F. Wang et al., 2020).

152 1.2. *Immunosenescence and its impact on age-related pulmonary diseases*

153 Immunosenescence is defined as the age-associated decline in the immune system capacity
154 to respond to infections and generate long-term immune memory (Cho and Stout-Delgado,
155 2020). As a consequence, older individuals are prone to infection, cancer, autoimmunity and
156 chronic inflammation, and exhibit a poor vaccine response (Al-Alawi et al., 2014; Fulop et al.,
157 2014; Murray and Chotirmall, 2015). Globally, immunosenescence has the following traits:
158 poor capacity to respond to new antigens, accumulation of memory T cells in detriment of a

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

162 Immunosenescence of *alveolar macrophages* causes a decrease in their total numbers and
163 capacity to perform phagocytosis and clearance of foreign particles, provoking susceptibility
164 to bacterial and viral infections causing CAP (Chen et al., 2020; Volkova et al., 2012; Wong
165 et al., 2017). It also diminishes the capacity of these cells to produce pro-resolution
166 mediators, such as resolvins (Arnardottir et al., 2014), antioxidant/detoxification factors in
167 response to cigarette smoke in COPD disease (Suzuki et al., 2008), or to clear away
168 apoptotic airway epithelial cells generated during COPD (Chen et al., 2020; Hodge et al.,
169 2003). Immunosenescence of airway mucosal *Dendritic Cells* (DCs) is reflected by lower
170 expression and function of Toll-like receptors (TLRs), decreased phagocytosis capacity, and
171 diminished/delayed migration potential towards draining lymph nodes upon activation
172 (Agrawal et al., 2007; Agrawal and Gupta, 2011; Volkova et al., 2012). In the context of viral
173 pneumonia, the capacity of DCs to prime naïve T cells against influenza is deficient due to a
174 delayed infiltration kinetics of DCs into the aged lungs, and a defect of DCs migration from
175 the lung into the draining lymph nodes (Valkenburg et al., 2012; Zhao et al., 2011). DCs also
176 display age-associated defects in their ability to prime CD8⁺ T cell responses through MHC-I-
177 dependent antigen presentation (Zacca et al., 2015), and inflammasome activation and
178 production of IL-1 β (Chen et al., 2020; Stout-Delgado et al., 2012). Immunosenescence of
179 *neutrophils*, the most abundant innate immune leukocyte, provokes an unregulated
180 production of superoxide, deficient phagocytosis (Chen et al., 2014; Cho and Stout-Delgado,
181 2020; Corberand et al., 1981) and deficient formation of neutrophil extracellular traps (NETs)
182 that correlates with defective bacterial clearance (Brinkmann and Zychlinsky, 2007).
183 Immunosenescence also impacts neutrophil migration to the lung in response to stimuli but
184 these cells tend to accumulate and prolong their stay in this organ (Kahlich et al., 1975).
185 Together, these age-related alterations in neutrophil functions can have devastating
186 consequences, as best exemplified in the current SARS-CoV-2 pneumonia epidemic (Barnes

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

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

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

223 1.3. Microbiota in the ageing lung

224 The microorganisms populating this tissue have a low density, which appears to be critical
225 for the maintenance of healthy lungs (Mathieu et al., 2018) and these bacteria can exert
226 distinct effect on the pathogenesis of lung diseases such as asthma (Mathieu et al., 2018;
227 Remot et al., 2017). Due to the difficulty to access resident lung microbiota, to date, no study
228 has been performed on lower respiratory tract microbiota in the elderly population and only
229 few studies have compared the composition of the upper respiratory tract microbial
230 ecosystem in the elderly to the one in younger adults (Table 1, (de Steenhuijsen Piters et al.,
231 2016; J.-J. Lee et al., 2019; Stearns et al., 2015; Whelan et al., 2014)). Advanced age
232 decreased the relative abundance of *Corynebacterium* and *Propionibacterium* in the nose
233 and of *Prevotella* in the oropharynx. Importantly, Whelan *et al.* demonstrated that, although
234 the microbiota from the anterior nares is distinct from that of the oropharynx in mid-aged
235 adults, this distinction is abolished in elderly subjects (Stearns et al., 2015), suggesting that
236 ageing in the upper airways is accompanied by a loss in the geodistribution of the microbial
237 ecosystem. Another study by the same group, comparing URT microbiota from children to
238 that of adults, reported similar high inter-individual variability, as was shown in elderly
239 individuals. Therefore, it is possible that the absence of a more stable URT microbiota in
240 these aged groups is related to a higher susceptibility to respiratory infections and other lung
241 diseases, such as asthma as seen in children for whom the prevalence of these diseases is

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

249 **Table 1: Summary of the results of publications comparing respiratory tract microbiome from elderly to**
 250 **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 ↗ <i>Streptococcus</i> (both locations)
	242	Publicly available data (NIH's Human Microbiome Project)	18–40	Anterior nares and throats		in anterior nares: ↘ <i>Corynebacterium</i> , <i>Propionibacterium</i> , <i>Staphylococcus</i> ↗ <i>Prevotella</i> , <i>Veillonella</i> in oropharynx: ↘ <i>Prevotella</i> , <i>Lachnospiraceae</i>
de Steenhuijsen (2016) (de Steenhuijsen Piters et al., 2016)	100	Elderly pneumonia (EP) patients	75.7	Oropharynx	HE vs. YH EP vs. HE & YP vs. YH	↗ <i>Rothia</i> and <i>Lactobacillus</i> ↘ <i>Prevotella</i> , <i>Veillonella</i> , <i>Leptotrichia</i>
	91	Healthy elderly (HE)	75.3			↗ overall bacterial density ↘ species richness (not in young cohorts) ↗ Shannon diversity indices (not in young cohorts) ↗ <i>Streptococcus (pseudo)pneumoniae</i> , several <i>Streptococcus</i> OTUs, <i>Rothia</i>
	27	Young adult pneumonia (YP) patients	46.4			↘ <i>Gemellales</i> , <i>Prevotella melaninogenica</i> , <i>Veillonella dispar</i> , <i>Parascardovia</i> and <i>Leptotrichia</i>
	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 AE vs. AA AA vs. HA	No change in diversity indices ↗ <i>Proteobacteria</i> ↘ <i>Propionibacterium</i> , <i>Corynebacteriales</i>
	30	Asthmatic elderly (AE)	72.5 ± 5.4			↘ <i>Staphylococcus</i> , <i>Propionibacterium</i> , <i>Moraxella</i>
	10	Healthy adults (HA)	25.4 ± 6.2			↗ <i>Proteobacteria</i>

	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 <i>Fusobacteria</i> and <i>Leptotrichia</i> associated with arterial stiffness in elderly subjects
	24	Young	29			

251

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

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

258 *2.1. Nutrition and cellular senescence*

259 As described above, at the cellular level, the ageing process, called senescence is
 260 characterized, among others, by shortening of telomeres and the SASP (Senescence-
 261 Associated Secretory Phenotype). One current area of interest is whether diet can influence
 262 senescence process. This has now been studied by many groups and reviewed recently
 263 (Balan et al., 2018), although no consensus has emerged. Some studies have reported a
 264 positive association between a longer telomere length, measured in leukocytes, and certain
 265 types of food, including nuts, seaweed, fruits or coffee, whereas consumption of alcohol, and
 266 red or processed meat was associated with a shorter leukocyte telomere length (Balan et al.,
 267 2018; Lee et al., 2015; Leung et al., 2014; Liu et al., 2016; Pavanello et al., 2011; Tucker,
 268 2018). Consumption of certain diets, foods and nutrients have also been positively or
 269 negatively associated SASP in different tissues (Sone and Kagawa, 2005; S.-Y. Wang et al.,
 270 2019; Yang et al., 2020). On the other hand, a meta-analysis from 2017 (Pérez et al., 2017),
 271 which included 533 participants under 9 different diets in 5 randomized controlled trials,
 272 showed that there was no effect of diet on telomere length. However, there was a high
 273 heterogeneity in the types, length of studies and in the dietary interventions, which might

274 have affected the conclusion of this meta-analysis. One of the hypotheses that could explain
275 how diet impacts senescence process is through the regulation of ROS production and
276 oxidative stress coming from endogenous and exogenous sources. Indeed, it is known, for
277 example, that unhealthy diets, such as high fat diets, can induce an increase in ROS
278 production in certain tissues (Matsuzawa-Nagata et al., 2008; Vial et al., 2011). Of interest, a
279 healthy diet with reduced calorie intake (calorie restriction diet – CR), reduced mitochondrial
280 activity and ROS production, and this has shown some promising results in certain studies.
281 In animals, CR diet delayed the onset on some ageing-associated diseases such as diabetes
282 (Cheng et al., 2017; Colman et al., 2009), cardiovascular diseases (Colman et al., 2009) or
283 cancer (Weindruch et al., 1986), and it even prolonged life in non-human primates (Colman
284 et al., 2014, 2009), although it did not appear to affect telomere length (Smith et al., 2011). In
285 humans, while such studies are difficult to implement, similar health benefits have been
286 reported in certain population, such as the Okinawan adult population. This population eats
287 an average of 17% less calorie-intake compared to that of the rest of Japan, and has a
288 higher rate of centenarian people and a lower mortality due to cardiovascular diseases,
289 cancer and other diseases around the globe (Kagawa, 1978; Suzuki et al., 2001). The
290 CALERIE 1 & 2 studies have also demonstrated the beneficial effect of a CR diet on general
291 health and the prevention of ageing associated diseases (Most et al., 2018; Redman et al.,
292 2018; Weiss et al., 2006). Interestingly, intermittent fasting has also been shown to reduce
293 insulin resistance and cholesterol levels in humans, suggesting that this type of diet could
294 also be beneficial against the development of ageing associated pathologies by modulating
295 oxidative stress associated with ageing (Harvie et al., 2013, 2011; Klempel et al., 2012;
296 Stekovic et al., 2019; Varady et al., 2015).

297 *2.2. Involvement of the microbiota in the effect of nutrition on ageing processes*

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

301 interactions between the constituents (Aguilera, 2019; David et al., 2014; Derrien and Veiga,
302 2017; Duncan et al., 2007; Ley et al., 2006; Muegge et al., 2011; Walker et al., 2011; Wu et
303 al., 2011). Consequently, the effect of particular diets on molecular and cellular processes
304 involved in ageing could be mediated by the modulation of microbiota.

305 *2.2.1. Impact of nutrition on microbiota*

306 Our diet feeds the microbiota by supplying substrates for microorganisms, especially non-
307 digestible sugars, known as prebiotics (Gibson et al., 2017). Food is also a source of
308 microorganisms, seeding our ecosystems in the gut and the lung. The overall microbial
309 biomass ingested per day has been estimated around 10^{10} (Derrien and van Hylckama Vlieg,
310 2015), ranging from 10^9 to 10^{12} in function of the diet considered. In addition to fermented
311 foods, that are especially rich in microorganisms, it is important to realize that raw food we
312 ingest (*e.g.*, fruits, vegetables) also contains their own microbial communities that could
313 impact the composition and functionality of gut microbiota. Thus, modifying the diet for
314 elderly people also impacts the microorganisms they ingest. Since the early 2010's, it is
315 known that these food microorganisms survive through the GI tract and associate, at least
316 temporarily, with the resident gut microbiota (David et al., 2014; Walker et al., 2011),
317 although whether they "durably" colonize the digestive tract remains uncertain (McNulty et
318 al., 2011).

319 Distinct types of food, such as non-digestible starch, and particular diets like the
320 Mediterranean diet, affect the microbiota composition in a specific manner. It has been
321 extensively reviewed in recent years (Barber et al., 2020; Burr et al., 2020; Dogra et al.,
322 2020; Fassarella et al., 2020; Kolodziejczyk et al., 2019; Vandeputte and Joossens, 2020).
323 Although there exists a very high inter-individual variability, due to host and microbe own
324 characteristics, the microbiota appears as a strong malleable therapeutic target that can be
325 reshaped using specific diets. For instance, a high-fat and low-fibre diet in mice decreased
326 microbiota composition in *Bacteroidetes* and increased *Firmicutes* and *Proteobacteria*
327 (Hildebrandt et al., 2009). The consumption of poly-unsaturated fatty acids increased

328 bacteria, such as *Bifidobacterium*, *Lachnospira*, *Roseburia* and *Lactobacillus*, in humans
329 (Watson et al., 2018). Of interest for the ageing population as they often show protein
330 deficiency, the source of this nutrient also affects the microbiota composition (Zhu et al.,
331 2015). Soybean and peanut proteins induced modulation of the abundance of beneficial
332 bacteria in the gut; a diet enriched with 20% peanut protein increased *Bifidobacteria*, and
333 reduced *Enterobacteria* and *Clostridium perfringens* in rats (Peng et al., 2015). On the other
334 hand, animal derived proteins induced a *Bacteroides* enterotype (Wu et al., 2011). Gut
335 bacteria can convert L-carnitine and phosphatidylcholine, which are present in red meats,
336 into trimethylamine N- oxide (TMAO), which is associated with the development of
337 cardiovascular diseases, linking, here as well, the impact of diet on microbiota and the host
338 physiology. Strikingly, a recent study showed that in older individuals, consumption of
339 Mediterranean diet was associated with specific changes in microbiota composition and
340 function; adherence to this diet was associated with a lower decline in microbiota diversity,
341 an increase in taxa negatively associated with inflammation and positively associated with
342 SCFA production (Ghosh et al., 2020).

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

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

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

367 *2.2.2. Impact of microbiota on cellular senescence*

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

383 the search for molecules promoting healthy ageing, certain bacterial metabolites can also
384 reduce or prevent senescent process. This is the case of secreted products from
385 *Lactobacillus fermentum*, for example, which protects the 3T3-L1 preadipocytes *in vitro*
386 against oxidative stress-induced senescence by inhibiting the mTOR pathway (Kumar et al.,
387 2019). Although the responsible molecules have not been identified in this case, this study
388 provided a *proof-of-concept* that metabolites from probiotics may possess anti-ageing
389 properties. Depending on the diet and type of food intake, gut microorganisms can also
390 produce a family of metabolites termed short-chain fatty acids (SCFA). These are end
391 products of bacterial fermentation that happens in the gut and play important roles at local
392 and distant sites. In 2012, O'Callaghan *et al.* showed that a red meat rich diet was linked to a
393 decreased telomere length in rat colonic cells and could be prevented by adding resistant
394 starch to the diet. Interestingly, they found an association between the absolute telomere
395 length and the caecal levels of two SCFAs, acetate and propionate (O'Callaghan et al.,
396 2012).

397 It is now well established that the gut microbiome plays an important role in the development
398 and maturation of the immune system throughout life. In healthy individuals, commensal
399 bacteria rarely cross the physical barrier constituted by the epithelial cells and the mucus
400 layer. However, when this happens, bacteria are rapidly killed by macrophages. Others can
401 survive inside DCs but these cells only go as far as the mesenteric lymph nodes, restricting
402 the bacterial challenge to the mucosal immune system (Macpherson and Uhr, 2004). As the
403 epithelium becomes leaky with age, it is inferred that more commensals or bacterial
404 components can cross that barrier and may induce aberrant immune responses (Man et al.,
405 2014; Thevaranjan et al., 2017). The immune system may then react against native
406 microflora as well as inappropriately control invading pathogens. Additionally, the decline in
407 gut microbiota diversity, observed in older individuals, may also impact the immune system
408 at the local and systemic levels. This could be due, at least partly, to the reduction in growth
409 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 Chevreton, 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 Chevreton, 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

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

440

441 *3.1. The anatomical continuum between the lungs and gut is more permissive to*
442 *exchanges in the elderly*

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

462 Moreover, microbiota from the gut, the nose and throat, have recently been shown to
463 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 (Duvall 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 ↘ <i>Segmented filamentous bacteria</i> (SFB) ↘ <i>Lactobacillus/Lactococcus</i> ↗ <i>Enterobacteriaceae</i> (<i>E. coli</i>)	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	↗ <i>Proteobacteria</i> ↘ <i>Eubacterium, Ruminococcus, Bifidobacterium</i> and <i>Roseburia</i> ↗ <i>Escherichia, Salmonella, Enterococcus, Veillonella</i>	N/A
Yu (2015) (Yu et al., 2015)	Mouse / Bacterial colony plate counts	Influenza A/FM1/1/47 20% Lethal Dose 50 intranasally	↘ <i>E. coli</i> ↘ Anaerobic bacteria ↗ <i>Bifidobacterium</i> and <i>Lactobacillus</i>	N/A
Deriu (2016) (Deriu et al., 2016)	Mouse / MiSeq Illumina	Influenza A /Puerto Rico/8/34 (PR8) – 200 PFU – intra-tracheal	↗ <i>Proteobacteria</i> ↗ <i>Escherichia</i>	↗ IFN-Is (<i>Ifnar1^{-/-}</i>) mice IAV leads to enhanced susceptibility to secondary enteric infections
	Mouse / 16S qPCR		↗ <i>Enterobacteriaceae</i> ↘ <i>Segmented Filamentous Bacteria</i>	N/A
Bartley (2017) (Bartley et al., 2017)	Mouse / Miseq Illumina	Influenza virus A/PR/8/34 (PR8), 400 EID ₅₀ intranasally	↗ <i>Proteobacteria</i> ↗ <i>Verrucomicrobia</i>	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 ↗ <i>Bacteroidetes</i> (<i>Bacteroidaceae</i>) ↘ <i>Firmicutes</i> (<i>Lachnospiraceae, Lactobacillaceae</i>)	↗ in MUC5AC provides a source of energy to <i>Bacteroidetes</i>
	Mouse / MiSeq Illumina	Influenza A/Eng/195/2009, 4 × 10 ⁴ PFU/ml	↗ <i>Bacteroidetes</i> (<i>Porphyromonadaceae</i>) ↘ <i>Firmicutes</i>	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	<p>↘ <i>Firmicutes</i> in small intestine at 7dpi</p> <p>↘ <i>Bacteroidetes</i> in small intestine at 7dpi</p> <p>No change in fecal bacteria</p>	infections
Sencio (2020) (Sencio et al., 2020)	<p>Mouse (C57BL/6J) /</p> <ul style="list-style-type: none"> • MiSeq Illumina 	<ul style="list-style-type: none"> • 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 	<p>↗ <i>Verrucomicrobia</i> (<i>Akkermansia</i>), <i>Cyanobacteria</i></p> <p>↗ <i>Parabacteroidetes</i> and <i>Odoribacter</i></p> <p>↘ <i>Bacteroidales</i> S24-7</p> <p>↗ <i>Clostridiales</i> (unaffiliated), <i>Ruminococcaceae</i>, and <i>Mogibacteriaceae</i></p> <p>↘ <i>Lachnospiraceae</i> family, <i>Dehalobacterium</i> and <i>Lactobacillus</i> genera</p> <p>↗ <i>Alphaproteobacteria</i> <i>Gammaproteobacteria</i> (<i>Escherichia</i> genus)</p> <p>↘ <i>Betaproteobacteria</i> (<i>Sutterella</i> genus)</p>	IAV infection leads to decreased food intake, less production of Short chain fatty acids, particularly acetate
<i>Bacteria</i>				
<i>Mycobacterium tuberculosis</i>				
Winglee (2014) (Winglee et al., 2014)	<p>Mouse (Balb/c) /</p> <p>454 FLX pyrosequencing</p>	<i>Mycobacterium tuberculosis</i> CDC1551 or H37Rv,, aerosol (Middlebrook inhalation exposure system)	<p>↘ Diversity</p> <p>↘ <i>Bacteroidetes</i></p> <p>↗ <i>Actinobacteria</i></p> <p>↗ <i>Lactobacillus</i></p> <p>↘ <i>Lachnospiraceae</i></p> <p>↘ <i>Ruminococcaceae</i></p>	N/A
Luo (2017) (Luo et al., 2017)	<p>Human (adults) /</p> <p>MiSeq Illumina</p>		<p>↘ <i>Bacteroidetes</i></p> <p>↗ <i>Proteobacteria</i> (<i>Escherichia</i>), <i>Actinobacteria</i> (<i>Collinsella</i>)</p> <p>↘ <i>Prevotella</i>, <i>Lachnospira</i>, <i>Roseburia</i>, <i>Coprococcus</i> (<i>Firmicutes</i>)</p>	N/A
Hu (2019) (Yongfei Hu et al., 2019)	<p>Human (adults) /</p> <p>HiSeq Illumina 2500</p>	<i>Mycobacterium tuberculosis</i>	<p>↘ Alpha-diversity</p> <p>↗ <i>Coprobacillus</i> bacterium and <i>Clostridium</i> <i>bolteae</i></p> <p>↘ <i>Haemophilus parainfluenzae</i>, <i>Roseburia</i> <i>inulinivorans</i>, <i>Eubacterium eligens</i>, <i>Roseburia</i> <i>hominis</i>, <i>Roseburia</i> <i>intestinalis</i>, <i>Megamonas</i> <i>unclassified</i>, <i>Eubacterium</i> <i>rectale</i>, <i>Ruminococcus</i> <i>obeum</i>, <i>Dora</i> <i>formicigenerans</i>, <i>Coprococcus</i> <i>sp</i>_ART55/1, <i>Megamonas</i> <i>funiformis</i>, <i>Sutterella</i> <i>wadsworthensis</i>, <i>Bifidobacterium</i> <i>adolescens</i>, <i>Megamonas</i> <i>hypermegale</i>, <i>Collinsella</i> <i>aerofaciens</i>, <i>Bifidobacterium</i> <i>longum</i>, <i>Akkermansia</i> <i>muciniphila</i>, <i>Megamonas</i> <i>rupellensis</i>, <i>Coprococcus</i> <i>comes</i>, <i>Lachnospiraceae</i> bacterium</p>	N/A

			1_157FAA, <i>Ruminococcus lactaris</i> , <i>Bifidobacterium pseudocatenulatum</i> , <i>Dorea longicatena</i>	
Hu (2019) (Yongfeng Hu et al., 2019)	Human (adults) / HiSeq 2500 Illumina	<i>Mycobacterium tuberculosis</i>	No significant difference	N/A
Huang (2019) (Huang et al., 2019)	Human (adults) / MiSeq Illumina	<i>Mycobacterium tuberculosis</i>	↗ <i>Bacteroidetes</i> ↘ <i>Bifidobacteriaceae</i>	Correlation between gut F/B ratio blood IL-1β
Li (2019) (Li et al., 2019)	Human (children) / MiSeq Illumina	<i>Mycobacterium tuberculosis</i>	↘ Diversity (Simpson index) ↗ <i>Enterococcaceae</i> , <i>Prevotellaceae</i> ↘ <i>Rikenellaceae</i> , <i>Bifidobacteriaceae</i> , <i>Lachnospiraceae</i> , <i>Ruminococcaceae</i> , ↗ <i>Enterococcus</i> , <i>Prevotella</i> ↘ <i>Faecalibacterium</i> , <i>Bacteroides</i> <i>Ruminococcus</i> , <i>Dorea</i>	N/A
Namasivayam (2019) (Namasivayam et al., 2018)	Rhesus macaques / Illumina NextSeq (V4 region)	<i>Mycobacterium tuberculosis</i> Erdman strain, <10 CFU, intra-bronchial instillation	Minor changes Severe diseases associated with: ↗ <i>Roseburia intestinalis</i> (family <i>Lachnospiraceae</i>), <i>Succinivibrio dextrinosolvens</i> , certain <i>Ruminococcaceae</i> , and <i>Weissella</i> (family <i>Leuconostocaceae</i>) ↘ <i>Streptococcus equinus</i> (family <i>Streptococcaceae</i>)	N/A
<i>Streptococcus pneumoniae</i>				
Dabrowski (2019) (Dabrowski et al., 2019)	Mouse (BALB/c) / MiSeq Illumina	<i>Streptococcus pneumoniae</i> , NCTC 7978, 10 ⁵ cfu	↗ <i>Lachnospiraceae</i> , <i>Ruminococcaceae</i> ↘ <i>Bacteroidales</i> S24-7, <i>Lactobacillaceae</i> , <i>Coriobacteriaceae</i>	N/A
Fungi				
Samuelson (2016) (Samuelson et al., 2016)	Mouse (C57BL/6j) / MiSeq Illumina	<i>Pneumocystis murina</i> (2 × 10 ⁶ cysts/mL (intratracheal))	↘ α-diversity ↗ <i>Lactobacillus</i> , <i>Ruminococcus bromii</i> ↘ <i>Turicibacter</i> , <i>Lachnospiraceae</i> <i>Oscillospira</i> ,	N/A

524

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

530 pathogens. As studies are sparse for certain types of pathogens such as fungi or certain
531 bacteria commonly responsible for pneumonia in elderly people, it is, at the time of writing,
532 impossible to identify specific patterns associated with specific types of pathogens.
533 Most studies that have searched for gut colonization of the respiratory pathogen have not
534 found any evidence that this occurs, suggesting that there exist other lines of communication
535 responsible for the dysbiosis observed in the gut. Mechanisms of action involved in
536 transducing the signal of infection from the lungs to the GI tract are not yet fully understood,
537 although certain pathways have been identified. For instance, Wang *et al.* showed that after
538 Influenza A virus (IAV) infection, lung-derived CD4⁺ T cells activate the CCL25-CCR9 axis to
539 induce the recruitment of CCR9⁺CD4⁺ T cells to the intestine and thus inducing gut
540 microbiota dysbiosis. Likewise, a recent study by Liu *et al.* showed that mast cells might also
541 be key players in transducing the signal of infection from the lungs to the gut (Liu *et al.*,
542 2019).

543 *3.3. From the gut to the lungs – Impact of gut microbiota and food intake/diet on lung* 544 *health*

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

611 (Haak et al., 2018). The effect of butyrate is not specific to viruses as it was effective in
612 increasing survival of mice infected with *K. pneumoniae* (Chakraborty et al., 2017). Acetate
613 protected mice against Respiratory syncytial virus (RSV) infection as observed by a lower
614 weight loss, and a decreased lung viral load and inflammation (Antunes et al., 2019). Galvao
615 *et al.* also demonstrated that acetate, *via* the activation of its receptor, free fatty acid receptor
616 2 (FFAR, also known as GPR43), was protective against *K. pneumoniae* infection also by
617 controlling bacterial load and inflammation levels (Galvão et al., 2018). Finally, the study by
618 Sencio *et al.* also reported that acetate protected against secondary lung infections. This
619 group primarily infected mice with IAV followed by a secondary pulmonary infection with *S.*
620 *pneumoniae*. They found that supplementation with acetate restored IAV-induced impairment
621 of alveolar macrophages bacterial killing activity as well as prolonged mice survival following
622 bacterial infection (Sencio et al., 2020). Taken together, these studies demonstrate the
623 protective function of gut microbial metabolites against respiratory infection.

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

638

639 4. DISCUSSION

640 As described in this review, recent studies have provided evidence for the modulation of
641 respiratory health by diets and/or shifts in microbiota composition and function (Sencio et al.,
642 2020; Trompette et al., 2018, 2014; Vaughan et al., 2019). These studies have mainly been
643 carried out on animal models at a young or adult age. The ageing process is influenced by
644 both intrinsic and external factors. In addition to replicative senescence, events along
645 people's lifespan might have long-lasting impacts on their own physiology, as well as on their
646 microbiota. Repetitive courses of antibiotics, for example, disrupt the gut microbial
647 ecosystem, and we can assume that it is also the case for the lung microbiota. Considering
648 the physiological characteristics of the elderly population, it is now important to investigate
649 the interactions between diet, gut and lung microbiota, and lung health and disease, in
650 models mimicking more closely the physiological changes happening in older human adults.
651 This would involve either aged wild-type animals or genetically modified animal models of
652 accelerated ageing. The *Terc*^{-/-} mice, for example, are deficient in the RNA subunit of the
653 telomerase, and have shown a higher susceptibility to bacterial pneumonia (Kang et al.,
654 2018), while the *Klotho*^{-/-} mice, which develop premature-ageing syndrome, also develop
655 emphysema (Nakatani et al., 2009). It also appears that the lines of communication between
656 the gut and the lungs might be enhanced by the impairment of the barrier function of both
657 epithelial structures. Establishing models that will mimic these features will allow the study of
658 the impact of the loss of topography of the microbiota in the susceptibility and pathogenesis
659 of pulmonary diseases. Interestingly, a loss of compartmentalisation of the microbiota has
660 been reported in chronically malnourished children (Vonaesch et al., 2018). Extrapolating to
661 elderly individuals, malnutrition could also lead to the loss of topography of the microbiota,
662 exacerbating the communication between the lung and the gut and thus increasing the
663 susceptibility to respiratory diseases. Although mammalian lungs from different species
664 share extensive characteristics, there exist differences, particularly between rodents and
665 humans, which can impact responses to inhaled particles and pathogens. This is particularly

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

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

687 It is well known that viral respiratory infections such as influenza, SARS or RSV, can cause
688 serious illness in elderly patients and are often associated with changes in gastro-intestinal
689 homeostasis and gut dysbiosis. Strikingly, older patients infected with SARS-CoV-2 who
690 were hospitalized, frequently presented comorbidities, with hypertension and T2D being
691 amongst the most prevalent ones (Guan et al., 2020; Richardson et al., 2020). These two
692 conditions have also been associated with gut dysbiosis (Gurung et al., 2020; J. Li et al.,
693 2017) and taken together, this points out to a central role of the microbiota in the physiology

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

699

700 **CONCLUSIONS**

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

708

709 **LIST OF ABBREVIATIONS**

710 AECII: Alveolar epithelial type II cells

711 AMDC: airway mucosal DC

712 ARDS: acute respiratory distress syndrome

713 ATP: adenosine triphosphate

714 BAL: bronchoalveolar lavage

715 BCR: B cell receptor

716 Blimp: B-lymphocyte-induced maturation protein

717 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: lipopolysaccharid
- 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- κ B: 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

780

781 **DECLARATIONS**

782 **Declaration of Competing Interests**

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

785 **Funding**

786 This work was supported by two grants from the *Agence Nationale de la Recherche*, [grant
787 numbers ANR-15-CE15-0012 (MMI-TB) to G. L-V and ANR-18-CE14-0011-03 (SevAsthma
788 children) to M.T].

789 **CRedit authorship contribution statement**

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

795 **Acknowledgements**

796 The authors thank Dr. M.A. Gray for his critical reading of the manuscript.

797

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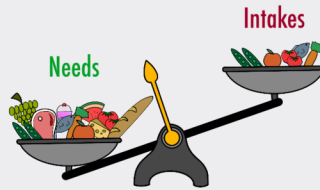
FIGURE LEGENDS

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.

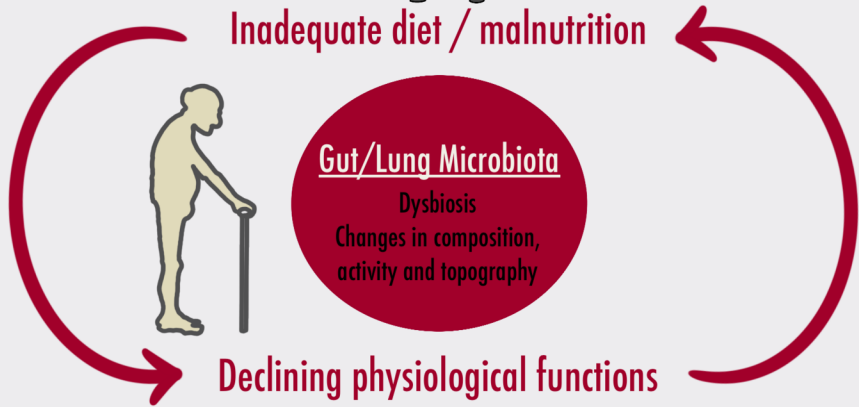
Figure 2: Hallmarks of the ageing lung and key cellular players involved in senescence.

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-aging
Increased frequency of
infections
Immune exhaustion

Musculoskeletal

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

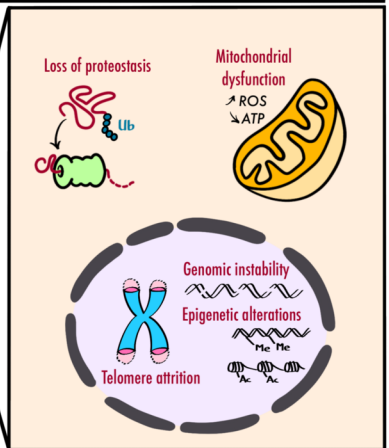
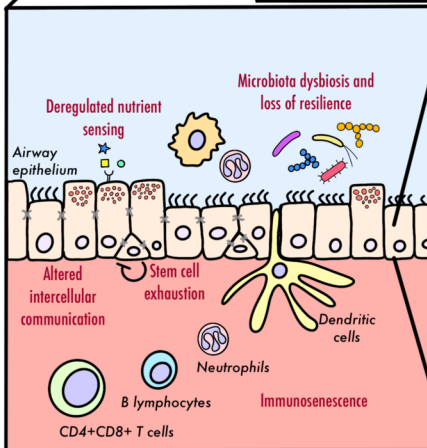
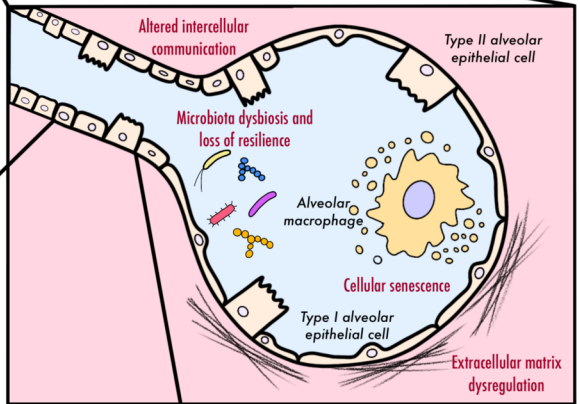
Aged lung

- Increased stiffness
- Decreased mucociliary clearance
- Loss in microbiota topography
- Enlarged alveoli

Age-related lung diseases

- COPD
- Irdiopathic 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)

Lungs
 10^2 (/mL broncho-
alveolar lavage)
 10^4 - 10^5 (/g tissue)

Blood and lymph
circulations

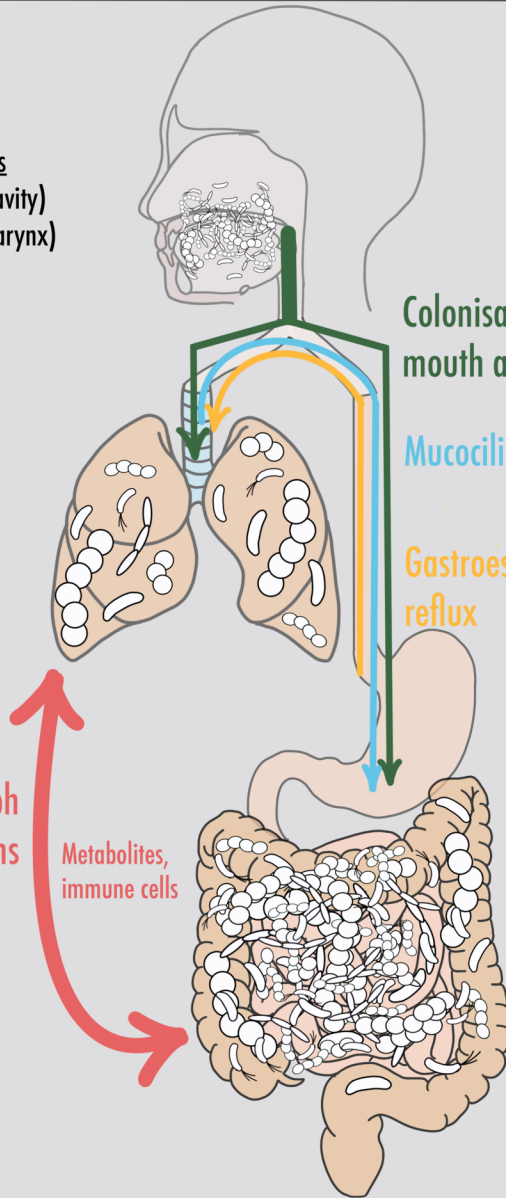
Metabolites,
immune cells

Colonisation from
mouth and nose

Mucociliary clearance

Gastroesophageal
reflux

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

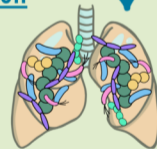
Reversibility

Gut eubiosis



Adequate
personalised
nutrition

Total or partial
irreversibility



Lung eubiosis

