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Is inflammageing influenced by the microbiota in the aged gut? A systematic review

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ABSTRACT

Ageing is characterized by a low-grade chronic inflammation marked by elevated circulating levels of inflammatory mediators. This chronic inflammation occurring in the absence of obvious infection has been coined as inflammageing and represents a risk factor for morbidity and mortality in the geriatric population. Also, with ageing, important perturbations in the gut microbiota have been underlined and a growing body of literature has implicated age-related gut dysbiosis as contributing to a global inflammatory state in the elderly. Notwithstanding, very little attention has been given to how gut microbiota impact inflammageing. Here, we investigate the available evidence regarding the association between inflammageing and gut microbiota during ageing. PubMed, Web of Science and Scopus were systematically screened, and seven relevant articles in animals or humans were retrieved. The animal studies reported that Parabacteroides, Mucispirillum, Clostridium and Sarcina positively associate with the pro-inflammatory MCP-1 while Akkermansia, Oscillospira, Blautia and Lactobacillus negatively correlate with MCP-1. Furthermore, "aged"-type microbiota were associated with increased levels of IL6, IL-10, Th1, Th2, Treg, TNF-α, TGF-β, p16, SAMHD1, Eotaxin, and RANTES; activation of TLR2, NF-κB and mTOR; and with decreased levels of cyclin E and CDK2. On the other hand, the study on humans demonstrated that bacteria of the phylum Proteobacteria exhibited a positive correlation with IL-6 and IL-8, while Ruminococcus lactaris et rel. portrayed a negative correlation with IL-8. We conclude that changes in "aged"-type gut microbiota are associated with inflammageing.

1. Introduction

The elderly population, particularly the oldest old group, is growing very rapidly. It was estimated that in 2020, for the first time in human history, people aged 60 and older will outnumber the children aged five and younger (https://www.thelancet.com/series/ageing). Moreover, by 2050, the elderly are expected to comprise more than one-fifth of the world's population (Lutz et al., 2008). These unprecedented demographic transformations have resulted in the emergence of new trends in epidemiology, with the rise of chronic diseases (Ezzati et al., 2002). Indeed, one of the most prominent manifestations of ageing - in both humans and non-human animals - is low grade chronic inflammation (LGCI), known as inflammageing (Fulop et al., 2017; Lencel and Magne, 2011; Chung et al., 2019). Serum levels of pro-inflammatory cytokines including, but not limited to, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are commonly elevated in the elderly when compared to young persons, even in healthy persons, in the absence of overt infection (Bruunsgaard and Pedersen, 2003). This LGCI is thought to underlie many age-related manifestations, including increased vulnerability for diseases, morbidity, and mortality (De Martinis et al., 2006). There is supportive evidence for a direct role of LGCI in the development of disability and dependence in elderly persons (Hubbard et al., 2009; Schmaltz et al., 2005). As a result, chronic inflammatory conditions commonly encountered in the geriatric population have become major health concerns.

Several possible sources of LGCI observed during ageing have been

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postulated, including, among others, cell senescence, dysregulation of innate immunity, and changes in gut integrity (Lasry and Ben-Neriah, 2015; Licastro et al., 2005; Buford, 2017). In the gut, the intestinal epithelial cells represent the first barrier against invading microorganisms. They secrete antimicrobial substances such as mucins and defensins, and are able to sense pathogens (via recognition by Toll-like receptors), sample them and transfer the information to immune cells (Miron and Cristea, 2012; Kraehenbuhl and Neutra, 2000). However, several studies have reported major alterations in immune responses of the aged gut in both humans and non-human animal models (Dicarlo et al., 2009; Biagi et al., 2013; Larbi et al., 2008; Simioni et al., 2007). For instance, a reduction in the secretion of mucin by intestinal epithelial cells and a greater permeability of mucosal membranes have been observed in older persons (Tran and Greenwood-Van Meerveld, 2013). This condition facilitates the entry of microorganisms into the mucosal layers, resulting in the release of heightened levels of lipopolysaccharides, which, in turn, may lead to pro-inflammatory signaling through pattern recognition receptors (Chassaing and Gewirtz, 2014; Cani et al., 2008; Cerf-Bensussan and Gaboriau-Routhiau, 2010; Mehal, 2013). In this perspective, increasing evidence has implicated age-related deterioration of the gut barrier against bacteria as contributing to inflammaging and age-related chronic health conditions (Chassaing and Gewirtz, 2014).

Emerging studies have shown that perturbations in gut microbiota configuration could play a role on mouse health and disease. Indeed, transplantation of fecal matter from twins discordant for obesity into germ-free (GF) mice resulted in variation of the mice's body composition measurements that were associated with differences in metatranscriptome profiles of the transplanted microbial communities', suggesting a role of the gut microbiota in obesity (Ridaura et al., 2013). Also, changes in aged gut microbiota in mice is associated with modifications in lipid classes and in fatty acid profile (in decreasing polyunsaturated fatty acids and in increasing monounsaturated fatty acid content) in the cortex, which has been reported to have a profound impact on brain physiology (Albouery et al., 2019). Another pathologic situation that is impacted by gut microbiota is Parkinson's disease, whose major risk factor is the clustering of α-synuclein in brain neurons. Mice that overexpressed α-synuclein developed α-synuclein clusters with corresponding defects in motor function and gut motility, while genetically-modified GF mice overexpressing α-synuclein show significantly fewer α-synuclein clusters. Moreover, fecal samples from Parkinson's patients increase motor dysfunction in mice, revealing the causative role of the gut microbiota in α-synuclein clustering and the resulting pathology (Sampson et al., 2016). More so, the sequence of bacterial 16S rRNA from fecal samples of transgenic mice expressing amyloid-β precursor protein - a critical risk factor for Alzheimer's disease - was found to have a remarkable shift in the gut microbiota as compared to non-transgenic wild-type mice. The colonization of GF amyloid-β precursor protein transgenic mice with microbiota from conventionally-raised amyloid-β precursor protein transgenic mice increased cerebral amyloid-β pathology, while colonization with microbiota from wild-type mice was less effective in increasing cerebral amyloid-β levels (Harach et al., 2017).

Also, in humans, dysbiosis in gut microbiome is known to be an important contributing factor of age-associated pathological states. Indeed, many pathological conditions including cardiovascular diseases, insulin resistance, diminished motor activity, and hepatic steatosis have been associated with gut dysbiosis (Nicholson et al., 2012; Burcelin et al., 2011). Moreover, age-related changes in gut microbiota have been shown to impact gut-brain axis in humans, thereby leading to diseases of the central nervous system such as anxiety, multiple sclerosis, depression, neurodegeneration and Alzheimer's disease (Collins et al., 2012; Luna and Foster, 2015; Friedland, 2015). The microbiome of older people suffering from Alzheimer's disease shows a lower proportion and prevalence of bacteria with potential to synthesize butyrate and a corresponding increase in the proportion of taxa that are responsible for proinflammatory states (Haran et al., 2019).

Thus far, our understanding of the effects of multiple deregulations in the gut microbiota in mediating inflammageing with advancing age is incomplete. In the aged population, there is reduction in the number of intestinal commensal bacteria that maintain immune tolerance in the gut (Claesson et al., 2012; Kumar et al., 2007), while most of the opportunistic bacteria whose numbers are generally elevated with age are known to stimulate intestinal inflammation (Kelly et al., 1994; Pamer, 2007). Indeed, Toward et al. (2012) reported an age-related decrease in the abundance of anti-inflammatory microbiota including *Bifidobacterium* spp. and *Faecalibacterium prausnitzii*. In contrast, the presence of pro-inflammatory microbiota, such as *Streptococcus* spp., *Staphylococcus* spp., *Enterococcus* spp., *and Enterobacter* spp. was found to increase with age (Toward et al., 2012). Also, a decline of bifidobacterial with a corresponding increase of Bacteroides has been observed with ageing (Hopkins et al., 2002; Hopkins et al., 2001; Biagi et al., 2010; Claesson et al., 2011). On the other hand, He et al. (2004) reported an age-related upregulation of Ruminococcus, Eubacterium, Lactobacillus and Enterococcus, contrasting with a reduction of Faecalibacterium and Bacteroides − both anti-inflammatory microbiota − reported to prevent intestinal inflammation (Mazmanian et al., 2008) through suppression of the pro-inflammatory IL-17 production and the induction of Foxp3 + regulatory T cells that produce IL-10 (Round and Mazmanian, 2010). In this framework, the current systematic review aimed at evaluating the literature on the effects of aged gut microbiota on inflammageing.

2. Method

2.1. Literature search

The literature databases including PubMed [search key: ((“Inflammation”[Mesh]) OR Inflammation) OR Interleukin*) OR Cytokine) OR infection) OR IL6) OR IL10) OR IL1) OR IL17) OR IL8) OR IL23) OR Interferon*) OR “tumor necrosis factor alpha”) OR “Granulocyte macrophage colony stimulating factor”) OR Lymphokine) OR Chemokine) OR Prostaglandin)) AND ((“Immunity”[Mesh]) OR Immunity) OR “Immune system”) OR (“T cell” OR “T cells”)) OR (“B cell” OR “B cells”)) OR (“dendritic cell” OR “dendritic cells”)) OR (“White blood cell” OR “White blood cells”)) OR Phagocyte) OR Macrophage) OR immunosenescence) OR Lymphocyte)) AND ((“Microbiota”[Mesh]) OR Microbiota) OR “Gut bacteria”) OR Prevotella) OR “Gut microbiota”) OR Bacteroides) OR Ruminococcus) OR “gut flora”) OR “Intestinal microbiota”) OR Microbiome) OR “gastrointestinal microbiota”) OR Enterotype) OR clostridium) OR clostridia) OR clostridioides)) AND ((“Aged”[Mesh]) OR “Older adult”) OR “Older adults”) OR senescence) OR geriatric) OR elderly) OR “Older people”) OR “Older peoples”)], Web of Science, and Scopus [search key: Inflammation OR Interleukin* OR Cytokine OR infection OR IL6 OR IL10 OR IL1 OR IL17 OR IL8 OR IL23 OR Interferon* OR “tumor necrosis factor alpha” OR “Granulocyte macrophage colony stimulating factor” OR Lymphokine OR Chemokine OR Prostaglandin AND Immunity OR “Immune system” OR “T cell” OR “T cells” OR “B cell” OR “B cells” OR “dendritic cell” OR “dendritic cells” OR “White blood cell” OR “White blood cells” OR Phagocyte OR Macrophage OR immunosenescence OR Lymphocyte AND Microbiota OR “Gut bacteria” OR Prevotella OR “Gut microbiota” OR Bacteroides OR Ruminococcus OR “gut flora” OR “Intestinal microbiota” OR Microbiome OR “gastrointestinal microbiota” OR Enterotype OR clostridium OR clostridia OR clostridioides AND Aged OR “Older adult” OR “Older adults” OR senescence OR geriatric OR elderly OR “Older people” OR “Older peoples”] were systematically screened for relevant articles that were published until January 2020 (last search on January 25th 2020).

Studies were included if they were written in English and analysed the relationship between inflammageing and gut microbiota either in humans or in animals. The definition of “older adults” age-range varies among authors (Ibrahim et al., 2010; Cleary and Skornyakov, 2017;

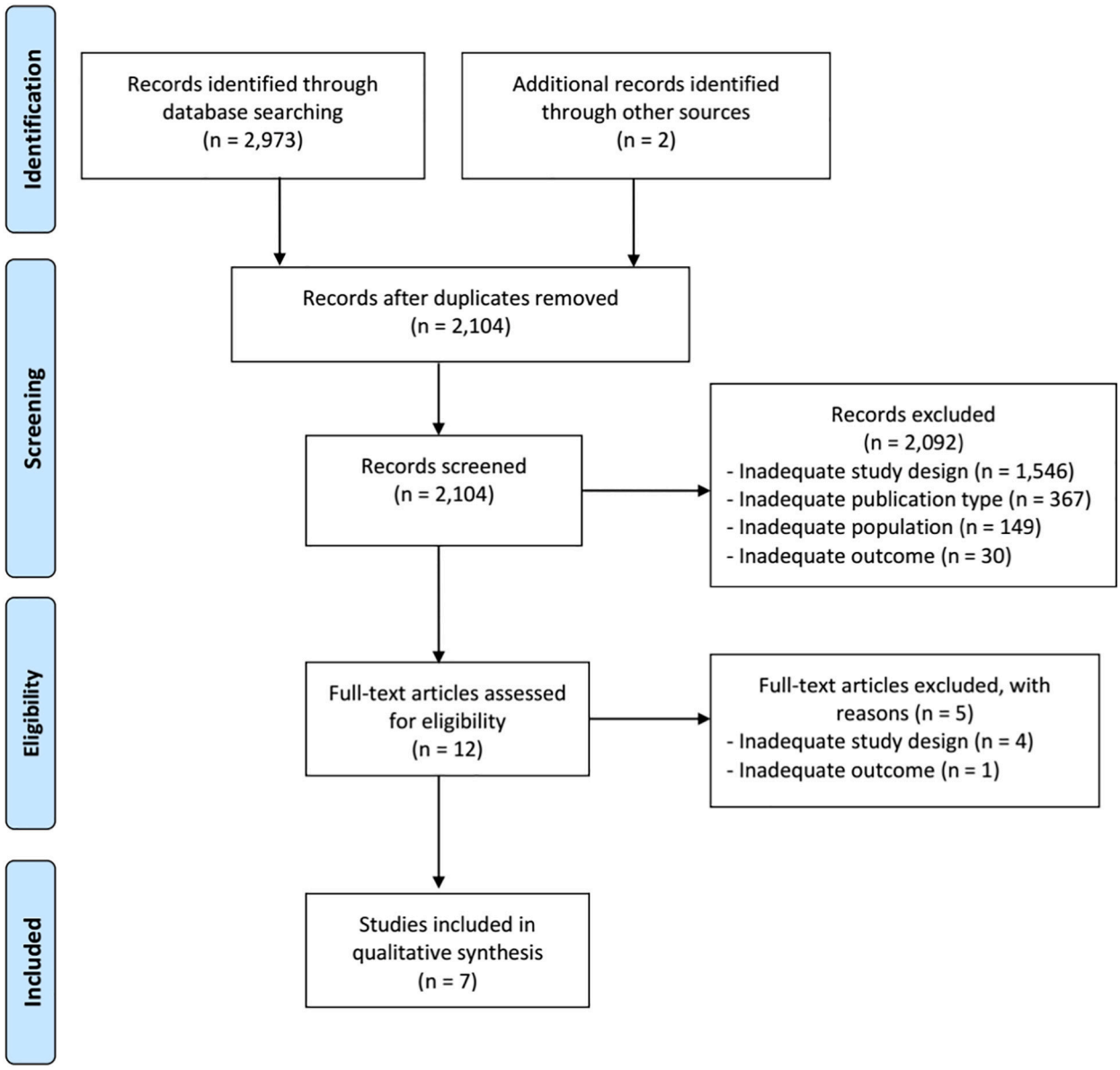

Fig. 1. PRISMA flow chart.

Eckardt, 2016; Birimoglu Okuyan and Bilgili, 2019). Therefore, to avoid missing our target population of elderly individuals, we also included this as a search term. Abstracts from conferences and observational studies were included while letters to editors, reviews, and comments to other articles were excluded. Two independent researchers – a professor at the department of Gerontology, of the Vrije Universiteit Brussel in Belgium and a PhD student at the same institution - assessed the eligibility of the articles for inclusion in this systematic review using Rayyan software (Ouzzani et al., 2016). A third researcher - a Geriatrician and former head of the Departments of Gerontology and Geriatrics (Universiteit Ziekenhuis Brussel) - was involved in case of disagreement and the article in question was included only if a consensual agreement was achieved. After analysis of the full texts, 5 articles were included. The reference lists of the 5 included articles were screened, which did not reveal additional relevant studies. After performing a forward search using articles that have cited the 5 articles included, 2 articles were added giving a total of 7 articles for the systematic review (see Fig. 1).

2.2. Quality assessment

The study on humans was analysed using the National Heart, Lungs and Blood Institute study quality assessment tools for observational cohort and cross-sectional studies (National Heart Lung and Blood Institute (NHLBI), 2014). Animal studies were analysed using the SYRCLE's risk of bias tool for animal studies (Hooijmans et al., 2014). Assessments were performed independently by two reviewers, and if assessments were conflicting, a consensus-based final score was assigned.

2.3. Data extraction

First, the main characteristics of the participants were identified (human or animal subjects, type of study population, age, gender). Next, the inflammatory markers that were analysed and the microorganisms of the gut were recorded.

Table 1
Summary of study results.

Author	Type of study	Participants	Mean age + SD	Inflammation	Gut microbiota	Results
Animal						
Conley et al. (2016)	Case control	5 young female C57Bl/6 mice 5 aged female C57Bl/6 mice	2 months 26 months	MCP-1	Bacteria in the gut: V4 region of 16S rRNA	Positively associate with MCP-1: Parabacteroides (0.84)[1], Mucispirillum (0.69)[1], Clostridium (0.69)[1] and Sarcina (0.69)[1] Negatively correlate with MCP-1: Akkermansia (−0.75)[1], Oscillospira (−0.78)[1], Blautia (−0.76)[1] and Lactobacillus (−0.75)[1]
Fransen et al. (2017)	Cohort	10 young C57BL/6JRccHsd female mice 10 young germ free old microbiota recipient female mice 10 young germ free young microbiota recipient female mice 5 young germ free control female mice 10 aged C57BL/6JRccHsd female mice	7–10 weeks 12–14 weeks 12–14 weeks 12–14 weeks 19–20 months	CD4+ Th, Treg, Th1, Th2, Th17 and TNF-α	Bacteria in the gut: V1 - V2 region of 16S rRNA genes	"Aged" microbiota: ↑ Th1, Th2, Treg in the spleen, Th1 in Peyer's patch and TNF-α ($p < 0.05$) ↑ activation of TLR2 ($p < 0.01$)
Kim et al. (2016)	Case control	8 young male C57BL/6 J mice 8 TLR4-deficient C57BL/10ScNJ young mice 8 old male C57BL/6 J mice	4 months 4 months 18 months	TNFα, IL-1β, and IL-6, p16, beclin-1, ATG7, LC3, NF-κB, mTOR, phosphorylated p65, p65, SAMHD1, cyclin E, CDK2, and β-actin proteins	Bacteria in the gut: V1 - V3 regions of 16S rRNA gene.	"Aged" microbiota: ↑ p16 and SAMHD1, activation of NF-κB and mTOR ($p < 0.05$) ↓ Cyclin E and CDK2 ($p < 0.05$)
Thevaranjan et al. (2017)	Cohort	WT young C57BL/6 mice WT C57BL/6 old mice Young SPF mouse Old SPF mice TNF−/− mice	10–16 weeks 18–22 months 8–14 weeks 18–22 months	IL6, TNF	Bacteria in the gut: V3 region of 16S rRNA	"Aged" microbiota: ↑ TNF and IL6 ($p < 0.05$)
Spychala et al. (2018)	Cohort	Young C57BL/6 male mice Aged C57BL/6 male mice	8–12 weeks 18–20 months	Circulating inflammatory cytokines: Multiplex assay kits	Bacteria in the gut: V4 to V5 region of 16S rRNA	"Aged" microbiota: ↑ IL6, TNF-α, Eotaxin, and RANTES ($p \leq 0.04$)
Zhang et al. (2019))	Longitudinal	Female Holstein cattle (n = 180): L1 (n = 60, 1st lactation) L3 (n = 60, 3rd lactation) L5+ [n = 60, 5th - 9th lactation)	NR	TNF-α, IL6, TGF-β, and IL-10: ST-360 Microplate Reader and cytokine diagnostic reagents	Bacteria in the gut: V3 - V4 region of 16S rRNA	"Aged" microbiota: ↑ TNF-α, IL6, TGF-β, and IL-10 ($p < 0.05$) Cellulosilyticum: ↑ TNF-α ($p < 0.01$)
Human						
Biagi et al. (2010)	Case control	21 centenarians (20 women, 1 man) 22 elderly (11 women, 11 men) genetically unrelated to the centenarians 20 young adults (9 women, 11 men) 21 elderly people - offspring of the centenarians (10 women, 11 men)	100.5 years 72.7 years 31 years 67.5 years	B lymphocytes, T lymphocytes, virgin T lymphocytes, memory T lymphocytes, NK cells IL-1a, IL-1b, IL-2, IL-6, IL-8, IL-10, IL-12p70, IFN-γ, TNF-α and TGF-β1	Bacteria in the gut: Total bacterial 16S rRNA genes	Positive correlation: Phylum Proteobacteria with either IL-6 or IL-8, (0.41 to 0.55)[2] p = NR Negative correlation: Ruminococcus lactaris et rel. with IL-8, (−0.44)[2] p = 0.0001

Note: 1 = Tau, 2 = Pearson correlation, NR = not reported, HITChip = Human Intestinal Tract Chip, IL = Interleukin, IFN = Interferon, TNF-α = Tumor necrosis factor alpha, TGF = Transforming growth factor, NK cells = Natural killer cells, MCP-1 = monocyte chemoattractant protein-1, Treg = Regulatory T cells, Th = T helper cells, TLR2 = Toll-like receptor 2, p16 = multiple tumor suppressor 1, ATG = Autophagy regulator, NF-κB = nuclear factor-kappa B, mTOR = mammalian target of rapamycin, SAMHD1 = sterile α-motif domain and HD domain-containing protein 1, CDK2 = Cyclin-dependent kinase 2, and RANTES = regulated on activation, normal T-cell expressed and secreted.

3. Results

3.1. Literature search

A potential total of 2973 articles were generated: 927 in PubMed, 921 in Web of Science, and 1125 in Scopus. Duplicates (n = 871) were removed and, excluding articles based on title and abstract, a total of 10 articles were retained. After analysis of the full texts, 5 articles were included. The reference lists of the included articles were screened, and a forward search was also performed using articles that have cited the included articles, bringing the total number to 7 articles. Six out of the seven selected articles correspond to animal studies (see Table 1), thus we focused our analysis on the animal studies and the human study has been introduced in the Discussion section.

3.2. Quality of study designs

The studies on animals amplified just portions of the gut microbiota (see Table 1) and were generally of good quality (Conley et al., 2016; Fransen et al., 2017; Kim et al., 2016; Thevaranjan et al., 2017; Zhang et al., 2019) except one (Spychala et al., 2018) which was of moderate quality. With regard to selection bias, 5 articles (Conley et al., 2016; Fransen et al., 2017; Kim et al., 2016; Thevaranjan et al., 2017; Zhang et al., 2019) showed appropriate methods of randomization and none reported adequate concealment of allocation (see Fig. 2). The groups were comparable at baseline in all included studies. In terms of performance bias, 3 studies reported on random housing (Conley et al., 2016; Kim et al., 2016; Zhang et al., 2019) and most of the investigators were not kept blinded to treatment allocation. Concerning detection bias, all the animals used in the studies were selected at random for outcome assessment. However, the outcome assessors were not blinded from knowing which intervention each animal received except for one of the studies (Thevaranjan et al., 2017). For attrition bias, all groups in each study were followed up for an equal length of time.

3.3. Results of the various studies

The animal studies were performed using mice from the United States of America (Conley et al., 2016; Kim et al., 2016; Thevaranjan et al., 2017; Spychala et al., 2018) and the Netherlands (Fransen et al., 2017), and cows from China (Zhang et al., 2019). The influence of the aged gut microbiota on the immune system was evaluated by Fransen et al. (2017), via the transfer of gut microbiota from young or old conventional mice to GF mice. They demonstrated that the aged microbiota induced higher frequencies of Th1, Th2, Treg in the spleen, and Th1 in Peyer's patch ($p < 0.05$) in GF mice, which received the "old" microbiota. Moreover, the expression of TNF-α was significantly elevated in the ileum after transferring microbiota of aged mice ($p < 0.05$; see Table 1). More so, "old" microbiota transfer lead to increased translocation of inflammatory bacterial products into the circulation, as GF mice that received "old" microbiota showed significantly higher activation of Toll-like receptor 2 ($p < 0.01$). Spychala et al. (2018) also tested the hypothesis that a heightened inflammatory response accompanies the aged microbiome when transplanted into young mice. Young mice with aged microbiota had a greater increase in proinflammatory cytokines following stroke compared to adult mice with young microbiota. Aged microbiota were associated with an increase in IL6, TNF-α, Eotaxin, and RANTES ($p \leq 0.04$), while the young microbiota were associated with an increased level of IL4 and granulocyte colony-stimulating factor ($p < 0.05$).

Thevaranjan et al. (2017) reported that intestinal permeability increases with age in mice due to age-related microbial dysbiosis that might drive intestinal permeability and decrease macrophage function. The microbial products that enter the bloodstream of aged mice trigger systemic inflammation leading to increased levels of TNF-α and IL6

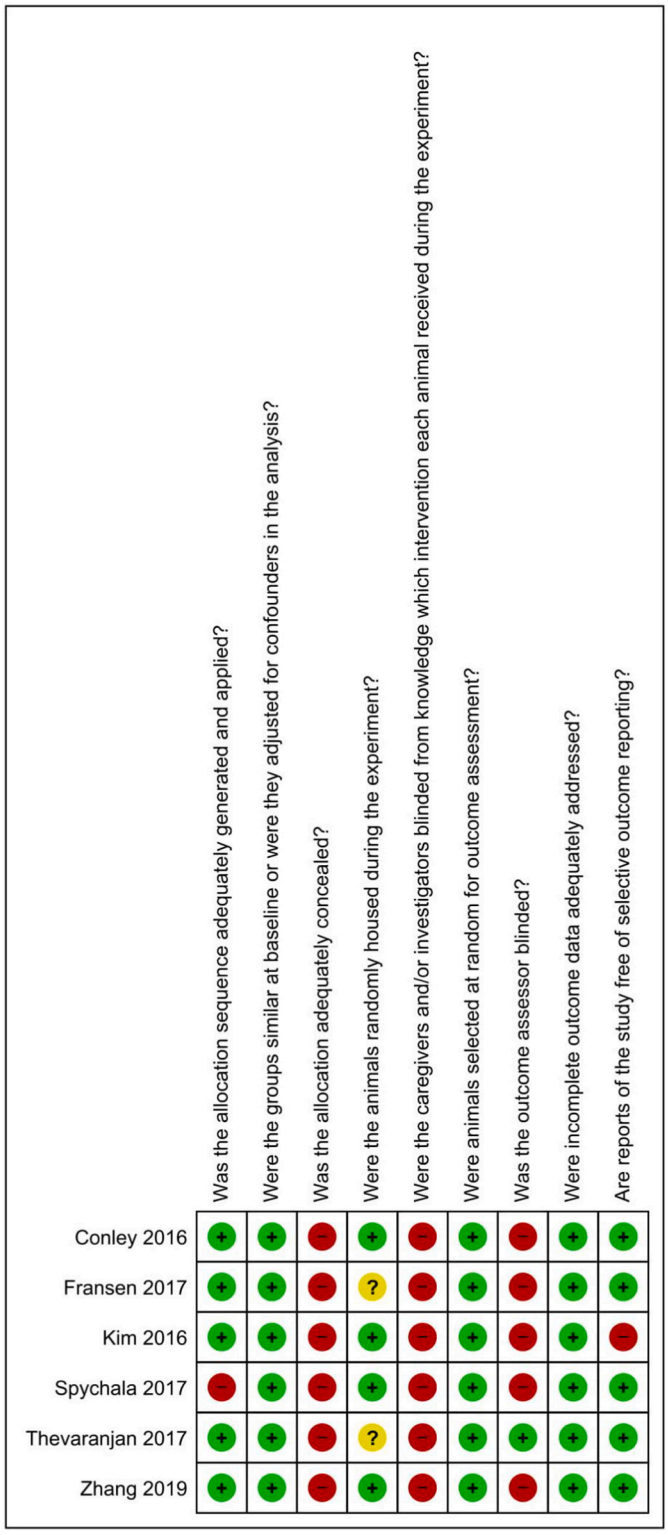

Fig. 2. Risk of bias summary Animal studies.
Animal studies were analysed using the SYRCLE's risk of bias tool for animal studies (Friedland, 2015). Green, red and yellow were respectively marked as Yes, No and Unclear on the SYRCLE checklist.

($p < 0.05$). Moreover, Conley et al. (2016) investigated the relationship between age, the microbiome, and serum monocyte chemoattractant protein-1 (MCP-1) as a surrogate marker of inflammation in a mouse model. It was anticipated that if a specific taxon interacts with the immune system, its relative abundance in the microbiome would be

associated with cytokine abundance. They tested for such associations by correlating Operational Taxonomic Units (OTUs) abundance and MCP-1. They identified 293 OTUs that significantly associated with MCP-1 status ($q < 0.15$, tau > 0.5). A total of 117 OTUs positively associated with MCP-1, with the strongest correlations from OTUs within Parabacteroides, Mucispirillum, Clostridium, and Sarcina (Kendall's tau = 0.84, 0.69, 0.69, and 0.69; respectively). Conversely, 176 OTUs negatively correlated with MCP-1. Those with the strongest negative correlations were within Akkermansia, Oscillospira, Blautia, and Lactobacillus (Kendall's tau = −0.75, −0.78, −0.76, and −0.75; respectively) (see Table 1).

The relationship between ageing and gut microbiota lipopolysaccharide-induced inflammation was investigated by Kim et al. (2016). The levels of p16 (a senescence marker), and cyclin E and CDK2 (cell cycle regulators) were measured. The expression of p16, SAMHD1, and the activation of NF-κB and mTOR were higher in aged mice, while the expression levels of cyclin E and CDK2 were rather decreased ($p < 0.05$).

Further, the bacterial communities in the rumen of cows were analysed by Zhang et al. (2019), with the aim of finding an explanation for the fragility of older dairy cows, and the relationship between the cow gut microbiota and inflammageing, as well as longevity. They observed a low-level inflammation among cows that have lactated for at least five different periods. The levels of all the measured cytokines - TNF-α, IL6, TGF-β, and IL-10 - were significantly higher in cows with a lactation period of five and above compared with those with first lactation period ($p < 0.05$). More so, Cellulosilyticum, which was more abundant in cows with a lactation period of five and above, was strongly and positively correlated to TNF-α ($p < 0.01$, see Table 1). A summary of the variation of key parameters of inflammation - as per the included studies - is shown in Table 2.

4. Discussion

The gut microbiota do not age per se, however, with ageing, important perturbations in the gut microbiota have been underlined and a growing body of evidence has implicated, among others, a reduced intestinal integrity as contributing to gut dysbiosis and its associated inflammation (Nagpal et al., 2018). Indeed, it has been speculated that the intestinal epithelium - that acts as a barrier between gut microbes and systemic circulation - might play a crucial role in the association of microbiota and inflammaging by allowing selective passage of essential substances, while preventing the entry of pro-inflammatory and other toxic substances into the body (Man et al., 2014; Nagpal and Yadav, 2017). In this light, a declined integrity of intestinal epithelium in old age could lead to leakage of gut bacteria in the systemic circulation eventually resulting in increased inflammatory triggers and perturbations in the intestinal microbiota. However, whether the primum movens of inflammageing is gut barrier ageing or microbiota deserves further investigation. For example Thevaranjan et al. (2017), demonstrated in a mouse model that ageing-associated gut microbial dysbiosis up-regulates intestinal permeability and as such contributes to the inflammatory state of the aged host. On the other hand, Sato et al. (2014), found that gut dysbiosis lead to the translocation of live gut bacteria into the blood of aged type-2 diabetes patients, predisposing the patients to various inflammatory diseases. Notwithstanding, these evidences suggest that alteration in the intestinal permeability and the gut microbiota might be associated with inflammaging and thus could be targeted to mitigate age-related inflammation.

To investigate whether “aged” type microbiota is a cause or consequence of inflammageing, aged micriobiota were transferred from old to young mice (Fransen et al., 2017; Spychala et al., 2018). This led to an exaggerated systemic inflammatory response, and higher frequencies of several T-helper cell subsets. Moreover, in young mice, the expression of several inflammatory markers, particularly TNF-α, increased, while short-chain fatty acids decreased, after receiving microbiota from old mice. TNF-α is well known for its role in pro-inflammatory responses and has been shown to increase intestinal epithelial permeability (Atarashi et al., 2013; Al-Sadi et al., 2013), provoking a further aggravation of inflammageing. Likewise, Thevaranjan et al. (Thevaranjan et al., 2017) demonstrated that exposure to microbial products including Toll-like receptor ligand or Th1 cytokines, such as TNF-α and IFN-γ, polarizes macrophages into the proinflammatory phenotype - leading to increased production of proinflammatory cytokines and reactive oxygen species - which ultimately contribute to the inflammatory state of the aged host (Oishi and Manabe, 2016). Moreover, Zhang et al. (2019) observed that dysbiosis of fecal microbiota of cows is related to inflammation. In their study, cellulosilyticum, a bacterial genus from the family of Lachnospiraceae - which was strongly and positively related to TNF- α - was more abundant in older cows. Also, the reconfiguration of older cows' microbiota led to changes in the metagenome: older cows metagenome contained more functions related to protein metabolism and fewer functions related to carbohydrate and lipid metabolism. Worth noting, the fermentation of proteins results in the production of toxic chemical substances while the loss of lipid and carbohydrate related genes may decrease the potential to generate beneficial compounds, such as short-chain fatty acids, which can exert anti-inflammatory effects through blocking the activation of NF-B (Zhang et al., 2019).

Serum MCP-1 - a surrogate marker of inflammation - was used by Conley et al. to further elaborate on the relationship between inflammageing and “aged” type gut microbiota (Conley et al., 2016). They observed that young and aged groups of mice had distinct gut microbiomes but also that aged mice exhibited elevated serum MCP-1, which correlated with “aged” type microbiota. The correlation between gut microbiome and serum MCP-1 in their study is indicative that the gut microbiome may play a modulating role in age-related immunological processes. Also, Kim et al. (2016) investigated the relationship between ageing and gut microbiota lipopolysaccharide (LPS)-induced inflammation and concluded that advancing age could cause gut microbiota dysbiosis, increase LPS production in the gut microbiota, increase the intestinal permeability, and thereby accelerate systemic inflammation. The identification of mechanisms that mediate age-related inflammation will be of significant impact on improving the quality of life of the elderly (Kim et al., 2016; Franceschi and Campisi, 2014).

On the other hand, the study on humans (Biagi et al., 2010) was of good quality with a low risk of bias; however, outcome assessors were not blinded (see Fig. 3). The study on humans was the only study that amplified the total bacterial 16S rRNA genes of the gut microbiota. The study analysed the gut microbiota of humans from Italy that might have been coexisting with their host for over 100 years and reported differences in terms of composition and diversity, which did not follow a linear relation with the age of the host. Indeed, the difference between the gut microbiota of young adults and elderly, separated by more than 40 years on average, was remarkably small when compared to that observed between centenarians and the younger elderly, separated by less than 30 years of life span. This comprehensive approach appears to indicate that the threshold for a switch toward an “aged” type of microbiota is situated around the age of 75–80 years. The analysis of the gut microbiota composition and the inflammatory parameters portrayed an upregulation of the proinflammatory cytokines in the peripheral blood of centenarians that correlated with changes in their gut microbiota profile. In particular, the increase of IL-6 and IL-8 was linked with an enrichment in Proteobacteria and a decrease in the levels of Ruminococcus lactaris et rel. (Biagi et al., 2010). This association between “aged” type gut microbiota and inflammageing was confirmed in studies in rodent models (Conley et al., 2016; Fransen et al., 2017; Kim et al., 2016; Thevaranjan et al., 2017; Zhang et al., 2019; Spychala et al., 2018), suggesting that age-related changes in the gut microbiota composition may be relevant in age-related inflammageing.

Studies have been carried out to alter the composition of the gut

Table 2
Summary of variation of inflammatory parameters as per the included studies.

Inflammatory parameters	Changes observed according to						
	Conley et al. (2016)	Fransen et al. (2017)	Kim et al. (2016)	Thevaranjan et al. (2017)	Spychala et al. (2018)	Zhang et al. (2019)	Biagi et al. (2010)
MCP-1	↑↓						
Treg		↑					
TLR2		↑					
Th1		↑					
Th2		↑					
Th17		↔					
TNF-α		↑	↔		↑	↑	↔
TGF-β						↑	
TGF-β1							↔
TNF				↑			
CD4+ Th		↔					
IL-1a							↔
IL-2							↔
IL-6			↔	↑	↑	↑	↑
IL-8							↑↓
IL-10						↑	↔
IL-1β			↔				↔
IL-12p70							↔
p16			↑				
Beclin-1			↔				
ATG7			↔				
LC3			↔				
NF-κB			↑				
mTOR			↑				
Phosphorylated p65			↔				
p65						↔	
SAMHD1			↑				
Cyclin E			↓				
CDK2			↓				
Eotaxin					↑		
RANTES					↑		
β-actin proteins			↔				
B lymphocytes							↔
T lymphocytes							↔
Virgin T lymphocytes							↔
Memory T lymphocytes							↔
NK cells							↔
IFN- γ							↔

Note: IL = Interleukin, IFN = Interferon, TNF-α = Tumor necrosis factor alpha, TGF = Transforming growth factor, NK cells = Natural killer cells, MCP-1 = monocyte chemoattractant protein-1, Treg = Regulatory T cells, Th = T helper cells, TLR2 = Toll-like receptor 2, p16 = multiple tumor suppressor 1, ATG = Autophagy regulator, NF-κB = nuclear factor-kappa B, mTOR = mammalian target of rapamycin, SAMHD1 = sterile α-motif domain and HD domain-containing protein 1, CDK2 = Cyclin-dependent kinase 2, and RANTES = regulated on activation, normal T-cell expressed and secreted.

microbiota - using probiotics - and to assess the possible role of such treatment in ameliorating gut immunity in aged mice and humans (Finamore et al., 2019; Nyangale et al., 2015). Treating aged mice with specific bacterial components has been found to restore the development of various important immune cells and to improve the inflammatory status (Zakostelska et al., 2011). *Bifidobacterium longum* Bar33 and *Lactobacillus helveticus* Bar13 probiotic mixture was demonstrated to modulated cells crucial for gut immune homeostasis by increasing regulatory T and B cells in the gut of probiotic-treated aged mice (Finamore et al., 2019). Also, the administration of probiotic mixture comprising of 8 Gram-positive bacterial strains induced a robust change in the composition of intestinal microbiota with an increase in the abundance of *Actinobacteria* and *Bacterioidete* in aged mice. Moreover, the expression of a large group of genes in brain tissue was also modulated, with evidence of a change in genes that have impact on inflammatory and neuronal plasticity processes (Distrutti et al., 2014). On the other hand, oral administration of heat-killed *Lactococcus lactis* (strain H61) to aged mice lead to the production of more interferon-gamma and IL-12, suggesting that administration of strain H61 altered immune responses (Kimoto-Nira et al., 2007). Further, *Lactobacillus rhamnosus* supplementation alleviated immunosenescence-associated Th1/Th2 imbalance in aged mice (Sharma et al., 2014). Furthermore, daily consumption of a probiotic (*Bacillus coagulans* GBI-30, 6086 (BC30); GanedenBC30) by adults aged 65–80 years increased beneficial groups of bacteria in the human gut, which lead to an increased production of anti-inflammatory cytokines (Nyangale et al., 2015). Aged individuals who consumed milk containing *Bifidobacterium lactis* for 6 weeks produced significantly enhanced levels of interferon-alpha upon stimulation of their peripheral blood mononuclear cells in culture (Arunachalam et al., 2000). Likewise, administration of a commercial probiotic cheese containing *Lactobacillus rhamnosus* HN001 and *Lactobacillus acidophilus* NSFM to healthy elderly volunteers increased the cytotoxicity of their natural killer cells (Ibrahim et al., 2010). However, these intervention studies were not included as part of this systematic review. Our literature search was designed to identify associations between inflammageing and “aged”-type gut microbiota. Consequently, our results reflect the present situation regarding the role of aged microbiota in inflammageing.

A limitation of this study is that the search was limited to three databases (i.e. Web of Science, Scopus and Pubmed). Other databases such as EMBASE could have reduced the risk of missing relevant studies. Notwithstanding, it has been reported that using EMBASE in addition to MEDLINE returns similar numbers of relevant references (Lefebvre et al., 2011).

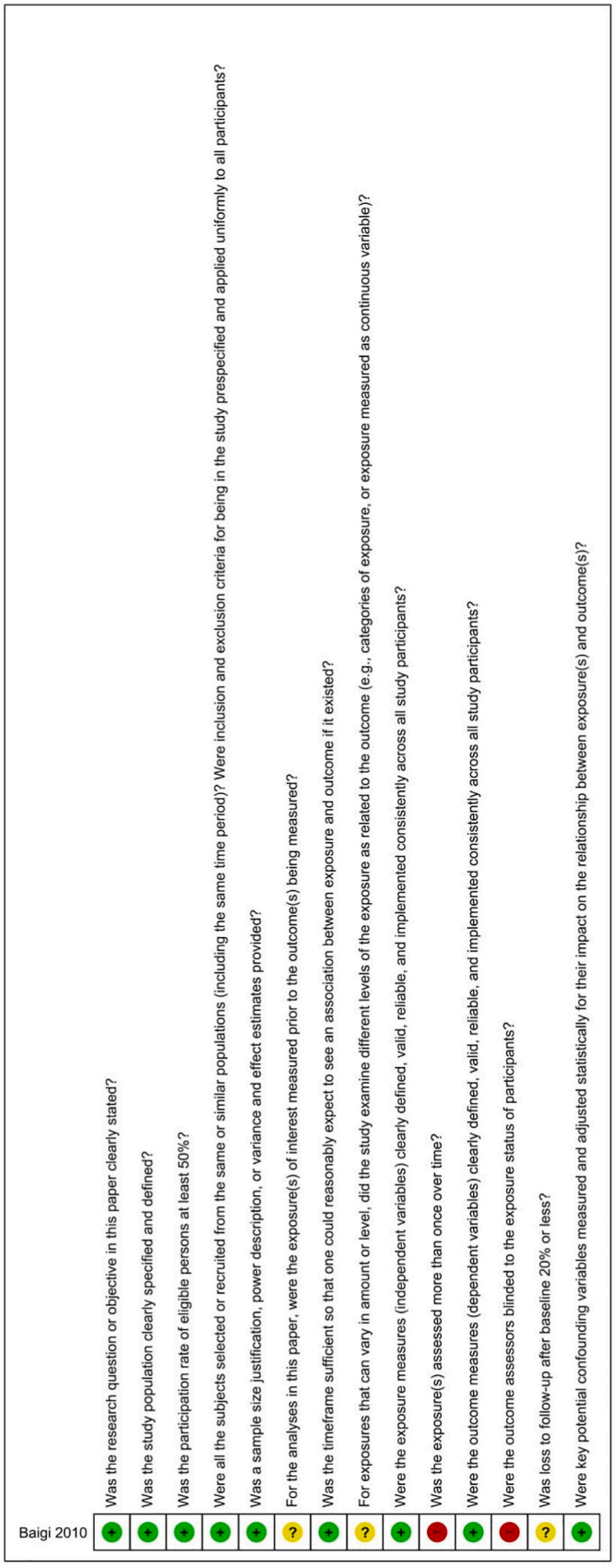

Fig. 3. Risk of bias summary Human study.
The study on humans was analysed using the National Heart, Lungs and Blood Institute (NHLBI) study quality assessment tools for observational cohort and cross-sectional studies (Luna and Foster, 2015). Green, red and yellow were respectively marked as Yes, No and Unclear on the NHLBI checklist.

5. Conclusion

In conclusion, ageing perturbs the gut microbiota with a shift in bacterial composition toward pro-inflammatory phenotypes. In the animal studies, age-related alteration in gut microbiota contributed to a chronic low-grade inflammatory state. Indeed, Parabacteroides, Mucispirillum, Clostridium and Sarcina positively associate with the pro-inflammatory MCP-1 while Akkermansia, Oscillospira, Blautia and Lactobacillus negatively correlate with MCP-1. Furthermore, "aged"-type microbiota were associated with increased level of IL6, IL-10, Th1, Th2, Treg, TNF-α, TGF-β, p16, SAMHD1, Eotaxin, and RANTES; activation of TLR2, NF-κB and mTOR; and with decreased level of cyclin E and CDK2. By the same token, the study on humans demonstrated that bacteria of the phylum Proteobacteria exhibited a positive correlation with IL-6 and IL-8, while Ruminococcus lactaris et rel. portrayed a negative correlation with IL-8. Hence, these aged-related changes in the gut microbiota can be considered as associated with inflammageing, which represents a risk factor for morbidity and mortality in the geriatric population. With the increasing life-expectancy and the exponential ageing of the population, the burden due to inflammageing is expected to increase steeply in the near future. Therefore, interventions directed at the composition of the gut microbiota might contribute to alleviate inflmmageing, improve well-being in older persons and reduce health-care related costs.

Author contributions

Conceptualization, Rose Njemini, Tony Mets, Ivan Bautmans; Data curation, Cabirou Mounchili Shintouo, Rose Njemini; Formal analysis, Cabirou Mounchili Shintouo, Rose Njemini, David Beckwee; Funding acquisition, Rose Njemini; Investigation, David Beckwee, Rose Njemini, Cabirou Mounchili Shintouo, Stephen M. Ghogomu, Jacob Souopgui; Methodology, David Beckwee, Cabirou Mounchili Shintouo, Rose Njemini, Lynn Leemans; Project administration Rose Njemini, Tony Mets; Resources, Rose Njemini, David Beckwee, Cabirou Mounchili Shintouo; Software, David Beckwee, Cabirou Mounchili Shintouo, Rose Njemini; Supervision, Rose Njemini, David Beckwee, Tony Mets; Validation Rose Njemini, Tony Mets; Roles/Writing - original draft, Cabirou Mounchili Shintouo, Rose Njemini; Writing - review & editing, Cabirou M. Shintouo, Tony Mets, David Beckwee, Ivan Bautmans, Stephen M. Ghogomu, Jacob Souopgui, Lynn Leemans, Henry D. Meriki, Rose Njemini.

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Declaration of competing interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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