Ageing Research Reviews 100 (2024) 102451

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Short review

The metabolic and endocrine impact of diet-derived gut microbiota metabolites on ageing and longevity

João R. Araújo [a,*], Cláudia Marques [a], Catarina Rodrigues [b], Conceição Calhau [a,c], Ana Faria [a,b]

[a] Nutrition & Metabolism, CINTESIS@RISE, NOVA Medical School, Faculdade de Ciências Médicas, NMS, FCM, Universidade NOVA de Lisboa, Lisboa 1169-056, Portugal
[b] Nutrition & Metabolism, CHRC, NOVA Medical School, Faculdade de Ciências Médicas, NMS, FCM, Universidade NOVA de Lisboa, Lisboa 1169-056, Portugal
[c] Unidade Universitária Lifestyle Medicine José de Mello Saúde by NOVA Medical School, Faculdade de Ciências Médicas, NMS, FCM, Universidade NOVA de Lisboa, Lisboa 1169-056, Portugal

ARTICLE INFO

Keywords:
Ageing
Gut microbiota
Metabolites
Diet
Host metabolic response

ABSTRACT

Gut dysbiosis has been recently recognized as a hallmark of ageing. At this stage of life, gut microbiota becomes depleted from bacteria involved in the production of short-chain fatty acids (SCFA), indole and its derivative indole-3-propionic acid (IPA), metabolites shown to improve host glycemic control as well as insulin sensitivity and secretion. Moreover, gut microbiota becomes enriched in pathobiont bacteria involved in the production of imidazole propionate, phenols and trimethylamine, metabolites that promote host insulin resistance and atherosclerosis. The magnitude of these changes is much more pronounced in unhealthy than in healthy ageing. On the other hand, a distinct gut microbiota signature is displayed during longevity, the most prominent being an enrichment in both SCFA and IPA bacterial producers. This short Review discusses, in an innovative and integrative way, cutting-edge research on the composition of gut microorganisms and profile of metabolites secreted by them, that are associated with a healthy and unhealthy ageing pattern and with longevity. A detailed description of the positive or detrimental metabolic effects, in the ageing host, of diet-derived gut microbial metabolites is provided. Finally, microbiota-targeted interventions that counteract gut dysbiosis associated with ageing, are briefly outlined.

1. Introduction

In the next 30 years, it is estimated that the number of individuals aged 65 years old or over (designated as "elderly") will nearly double, reaching 1 in 6 people worldwide by 2050 (United Nations, 2019). From a biological point of view, ageing is defined as the progressive loss of homeostasis, impaired organ function and vulnerability to death (López-Otín et al., 2013). Recently, it has been proposed that changes in the composition of gut microorganisms and in the profile of metabolites produced and secreted by them (gut dysbiosis), constitutes 1 of the 12 cellular and molecular hallmarks of ageing (López-Otín et al., 2023). Taking this into consideration, and the fact that gut dysbiosis contributes to the dysregulation of host physiological functions, increasing the risk of disease (Canfora et al., 2019), this short Review aims to describe, in an integrative way, the composition and metabolic function of the gut microbiota associated with a healthy and unhealthy ageing pattern and with longevity. Particular emphasis is given to gut microbial metabolites produced from dietary carbohydrates (including short-chain fatty acids) and proteins (including indole and its derivatives, imidazole propionate, phenols, hydrogen sulfide and trimethylamine) and how changes in their levels, during healthy and unhealthy ageing, impact host metabolic and endocrine functions. Finally, in the last part of this Review, the therapeutic potential of microbiota-targeted interventions that promote healthy ageing and longevity is outlined.

2. Factors affecting the gut microbiota during ageing

The composition and metabolic function of the gut microbiota of

Abbreviations: IPA, indole-3-propionic acid; GLP-1, glucagon-like peptide 1; SCFA, short-chain fatty acids; TMA, trimethylamine; TMAO, trimethylamine *N*-oxide.

* Correspondence to: NOVA Medical School, Faculdade de Ciências Médicas, NMS, FCM, Universidade NOVA de Lisboa, Campo Mártires da Pátria 130, Lisboa 1169-056, Portugal.
E-mail addresses: joaoricardo.araujo@nms.unl.pt (J.R. Araújo), claudia.sofia.marques@nms.unl.pt (C. Marques), catarina.rodrigues@nms.unl.pt (C. Rodrigues), ccalhau@nms.unl.pt (C. Calhau), ana.faria@nms.unl.pt (A. Faria).

https://doi.org/10.1016/j.arr.2024.102451
Received 21 February 2024; Received in revised form 16 July 2024; Accepted 6 August 2024
Available online 9 August 2024

elderly individuals is influenced by several intrinsic and extrinsic factors (reviewed by Ghosh et al. (2022)). One of the most important intrinsic factors is the deterioration of gastrointestinal tract physiological functions including: a) the reduction of smell, taste and masticatory capacities, b) alterations in peristaltic movements, c) the reduction or absence of gastric acid secretion, d) the decrease in the activity of digestive enzymes and nutrients absorption, and e) the decline of intestinal immune function (Ghosh et al., 2022). Another important intrinsic factor is the development of age-related diseases in particular frailty - a state of decreased reserve and function resulting in increased vulnerability to adverse outcomes upon exposure to stressors (Fried et al., 2021) – as well as cardiometabolic, neoplastic, musculoskeletal, cognitive, neurodegenerative and infectious diseases (Ghosh et al., 2022). Concerning extrinsic factors, these include a reduction in diet quality, the use of multiple drugs, physical inactivity and changes in social environment (*e.g.* living in an institutional accommodation or at home) (Ghosh et al., 2022). Although the extent to which each of these factors contribute to shape the gut microbiota during ageing is still unclear, their modulation, particularly by diet, may constitute a strategic opportunity to correct gut dysbiosis associated with ageing (DeJong et al., 2020).

3. Gut microbiota composition during ageing

Compared with young and middle-aged individuals, the gut microbiota of elderlies (aged between 65 and 80 years old) shows a distinct and unique composition (Ghosh et al., 2020a; Wilmanski et al., 2021) characterized by: a) a decrease in microbial species diversity (Hopkins, 2001; O'Toole and Jeffery, 2015; Salazar et al., 2019), b) a depletion of beneficial symbiotic bacteria belonging to *Prevotella*, *Faecalibacterium*, *Eubacterium*, *Lachnospira*, *Roseburia*, *Coprococcus* and *Bifidobacterium* genera (Ghosh et al., 2022; O'Toole and Jeffery, 2015; Salazar et al., 2019; Zhang et al., 2021), c) an enrichment in "potentially" beneficial bacteria (*i.e.* with less consistent health benefits compared to the previous ones) including *Akkermansia*, *Christensenellaceae*, *Butyricimonas*, *Butyrivibrio, Odoribacter, Oscillospira* and *Barnesiellaceae* (Ghosh et al., 2022; O'Toole and Jeffery, 2015; Salazar et al., 2019), and d) a higher abundance of pathobionts (Ghosh et al., 2022) - microorganisms that are benign under physiological gut conditions but become potentially pathogenic under altered gut conditions (*e.g.* an increase in pH and/or a decrease in motility and enzymatic activity) - such as *Eggerthella*, *Bilophila*, *Fusobacteria*, *Streptococcus, Desulfovibrio, Escherichia, Campylobacter* and certain *Clostridium* species (*e.g. C. hathewayi, C. scindens* and *C. bolteae*) (Ghosh et al., 2022; O'Toole and Jeffery, 2015; Salazar et al., 2019; Zhang et al., 2021).

Unhealthy ageing, typically defined by the presence of chronic age-related diseases in the elderly (Ghosh et al., 2022), is usually associated with a higher magnitude of both depletion of beneficial bacteria and enrichment of pathobionts, and a lower magnitude of enrichment of "potentially" beneficial bacteria (Ghosh et al., 2022). In contrast, a lower magnitude of both depletion of beneficial bacteria and enrichment of pathobionts and a higher magnitude of enrichment of "potentially" beneficial bacteria, is associated with healthy ageing (Ghosh et al., 2022), typically defined by the absence of chronic age-related diseases in the elderly (Rowe and Kahn, 1987). Although healthy ageing is not necessarily equivalent to longevity, *i.e.* the property of living until or close to the maximal human lifespan, several studies have been conducted on centenarians (individuals aged 100 years old or over) in order to potentially identify specific gut microbiota signatures associated with an extended healthy lifespan (Biagi et al., 2016; DeJong et al., 2020; Ghosh et al., 2022; Kim et al., 2019; Kong et al., 2019, 2016; Sato et al., 2021; Tuikhar et al., 2019; Wu et al., 2019). Compared to younger elderly and/or middle-aged individuals, the gut microbiota of centenarians is generally characterized by a higher diversity of bacterial species (Kong et al., 2019, 2016; Sato et al., 2021), and a greater abundance of beneficial *Bifidobacterium* and *Lactobacillus* and of "potentially" beneficial *Akkermansia, Christensenellaceae, Lachnospira, Butyricimonas, Odoribacter, Oscillospira* and *Methanobrevibacter* (Biagi et al., 2016; Kim et al., 2019; Kong et al., 2019, 2016; Sato et al., 2021; Tuikhar et al., 2019; Wu et al., 2019). However, a lower abundance of beneficial *Faecalibacterium, Coprococcus, Roseburia* and *Eubacterium* has been observed in this long-lived population (Kim et al., 2019; Kong et al., 2019; Sato et al., 2021; Tuikhar et al., 2019; Wu et al., 2019). Although this microbiota signature is similar across different centenarian populations, such as those from Italy (Wu et al., 2019), China (Kong et al., 2019, 2016), India (Tuikhar et al., 2019), Japan (Sato et al., 2021) and Korea (Kim et al., 2019), there are some differences between them, particularly regarding the most prevalent bacterial genera. This may reflect their distinct geographical locations, genetic backgrounds, dietary habits, and nutritional, cognitive and functional states as well (Wu et al., 2019).

4. Gut microbiota metabolic function during ageing

Although the majority of studies elucidated the composition rather than the metabolic function of the gut microbiota during ageing (see Section 3.), metabolites derived from the microbial metabolism of non-digestible dietary compounds have recently gained importance and visibility, as these have been shown to beneficially or detrimentally impact host energy and nutrient metabolism (Fig. 1 and Table 1) (Canfora et al., 2019; Fan and Pedersen, 2021; Wilmanski et al., 2021). Diet-derived microbial metabolites can be detected in feces, serum, urine and/or cerebrospinal fluid (Lavelle and Sokol, 2020), and alterations in their concentration in elderly individuals robustly correlate with changes in their gut microbiota composition (Wilmanski et al., 2021). Therefore, these metabolites have been proposed as useful biomarkers of gut microbiota signatures associated with healthy or unhealthy ageing (Ghosh et al., 2022; Salazar et al., 2019).

4.1. Short-chain fatty acids production

Acetate, propionate and butyrate are the main metabolic end-products resulting from non-digestible carbohydrate fermentation by the gut microbiota (Lavelle and Sokol, 2020). These short-chain fatty acids (SCFA) exert several metabolic and endocrine effects in the host (Fig. 1), in particular the regulation of glycemic response (Tolhurst et al., 2012), appetite (Chambers et al., 2015; Freeland and Wolever, 2010; Frost et al., 2014; Larraufie et al., 2018) and energy expenditure (Chambers et al., 2018; Gao et al., 2009; Sahuri-Arisoylu et al., 2016), mainly through the activation of specific free fatty acids receptors (Lavelle and Sokol, 2020) and/or induction of epigenetic modifications (*e.g.* histone acetylation) (Table 1) (Barrès and Zierath, 2016). SCFA regulate the glycemic response by stimulating gut enteroendocrine L cells to secrete glucagon-like peptide 1 (GLP-1) which, after being released into the systemic circulation, promotes insulin secretion in pancreatic β-cells, thereby lowering postprandial glycemia (Tolhurst et al., 2012). In addition, by up-regulating gluconeogenesis in enterocytes, propionate and butyrate prevent an hepatic overproduction of glucose and, consequently, its release into the blood circulation, thereby reducing the risk of hyperglycemia (De Vadder et al., 2014; Kimura et al., 2013). Regarding appetite regulation, propionate and acetate have been shown to stimulate the secretion of YY peptide (Freeland and Wolever, 2010; Larraufie et al., 2018) and GLP-1 (Freeland and Wolever, 2010) by gut enteroendocrine L cells, and leptin by adipocytes (Xiong et al., 2004). After crossing the blood-brain barrier, these three hormones activate hypothalamic pro-opiomelanocortin neurons responsible for generating satiety signals, resulting in appetite reduction (Chambers et al., 2015; Frost et al., 2014). Concerning energy expenditure, although not completely understood, SCFA seem to increase white adipose tissue energy expenditure by promoting thermogenesis and fatty acids beta-oxidation in white adipocytes (Chambers et al., 2018; Gao et al., 2009; Sahuri-Arisoylu et al., 2016), thereby preventing adipose mass accumulation. As a whole, this evidence suggests that

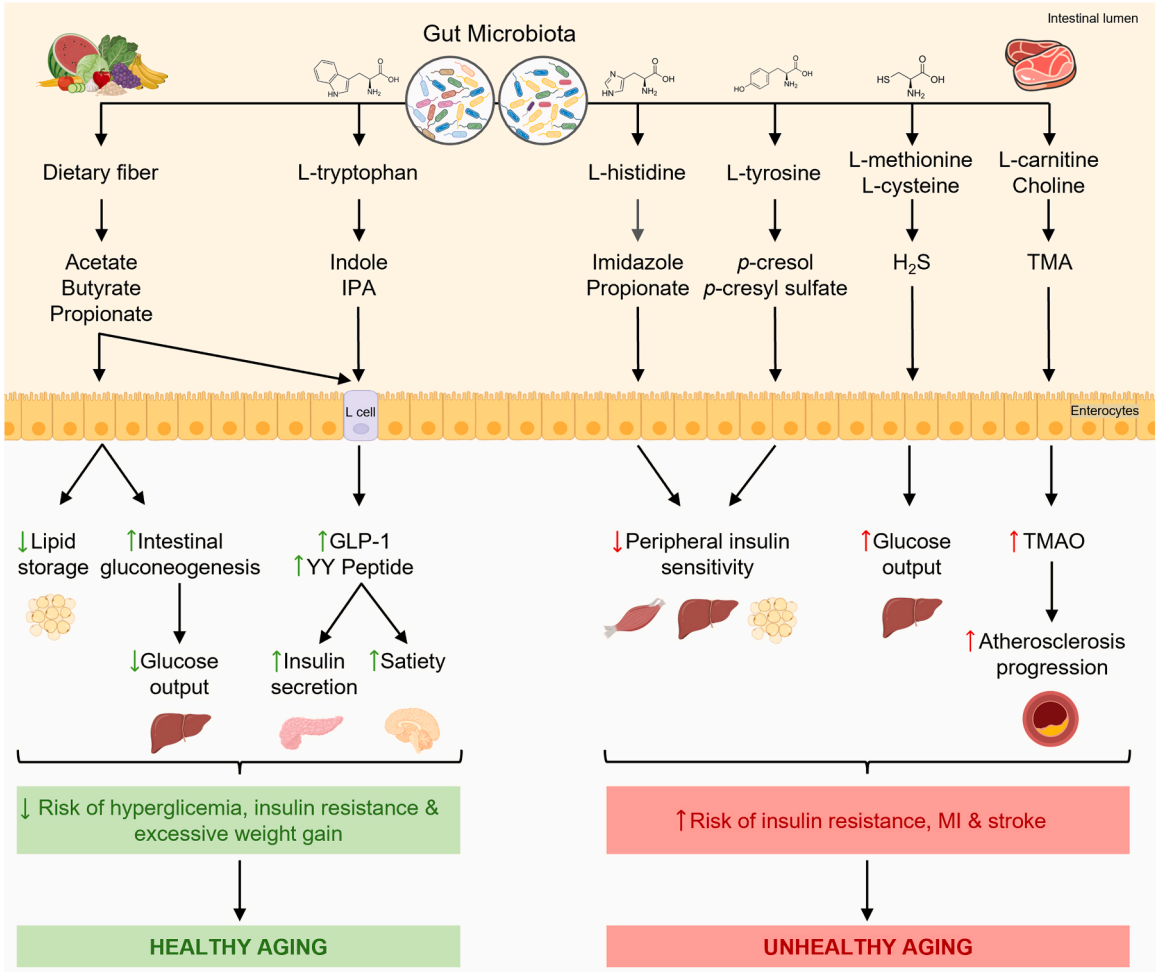

Fig. 1. Diet-derived gut microbiota metabolites beneficially or detrimentally impact metabolic and endocrine functions in the ageing host. Short-chain fatty acids, indole and indole-3-propionic acid improve glycemic control and insulin sensitivity and secretion - being associated with healthy ageing - while imidazole propionate, phenols and trimethylamine promote insulin resistance and atherosclerosis - being associated with unhealthy ageing. Abbreviations: glucagon-like peptide 1 (GLP-1), hydrogen sulfide (H_2S), indole-3-propionic acid (IPA), myocardial infarction (MI), trimethylamine (TMA) and trimethylamine *N*-oxide (TMAO).

SCFA may exert a preventive and therapeutic role against chronic metabolic diseases, in particular obesity and type 2 diabetes (Fig. 1) (Canfora et al., 2019).

In comparison with young and middle-aged individuals, a reduction in fecal and serum concentrations of butyrate, acetate and propionate have been observed in elderlies (Rampelli et al., 2013; Salazar et al., 2019; Sato et al., 2021), most probably due to their gut microbiota depletion from the SCFA' main bacterial producers: the beneficial *Prevotella, Faecalibacterium, Roseburia, Eubacterium* and *Bifidobacterium* (Lavelle and Sokol, 2020; Rampelli et al., 2013; Salazar et al., 2019; Sato et al., 2021). Although the depletion of these bacteria could be compensated by the enrichment in "potentially" beneficial SCFA-producing bacteria belonging to *Akkermansia*, *Butyricimonas*, *Butyrivibrio, Odoribacter* and *Oscillospira* genera, these are not core SCFA producers (Ghosh et al., 2022; O'Toole and Jeffery, 2015; Salazar et al., 2019). Moreover, low fecal levels of SCFA, in particular butyrate, were found to strongly correlate with biomarkers of frailty in elderly individuals (Claesson et al., 2012; Ghosh et al., 2020a), most probably reflecting the greater depletion of beneficial butyrate-producing bacteria and lesser enrichment of "potentially" beneficial butyrate-producing bacteria associated with unhealthy ageing (Ghosh et al., 2022). On the other hand, gut microbiota production (Wu et al., 2019) and, consequently, fecal concentrations (Cai et al., 2016) of butyrate, acetate and propionate were found to be higher in healthy centenarians compared to both healthy elderly (aged between 70 and 99 years old) and young adult individuals. These observation suggest that fecal levels of SCFA may be regarded as a promising biomarker of a gut microbiota pattern associated with healthy ageing and longevity (Table 1) (Wu et al., 2019). Future studies are however necessary to establish the fecal SCFA threshold concentration characteristic of that gut microbiota pattern.

4.2. *Amino acid metabolites production*

Compared to the fermentation of non-digestible carbohydrates, the metabolism of non-digestible proteins and amino acids by the human gut microbiota yields a more diverse range of metabolites, including indole and its derivates, imidazole propionate, phenols, hydrogen sulfide and amines (Canfora et al., 2019; Khan et al., 2014; Lavelle and Sokol, 2020). Indole and its derivative indole-3-propionic acid (IPA) can be produced from the essential aromatic amino acid tryptophan, via the indole pathway (Lavelle and Sokol, 2020). Both metabolites, but specially IPA, have been demonstrated to regulate the glycemic response by stimulating GLP-1 secretion in gut enteroendocrine L-cells (Chimerel et al., 2014) (as described for SCFA), being still unclear if this effect depends or not on the activation of aryl hydrocarbon receptors, of which both indole and IPA are potent agonists (Fig. 1) (Dong and Perdew, 2020). Notwithstanding, elevated serum concentrations of IPA were found to be associated with improvements in insulin secretion and sensitivity and, consequently, with a lower risk of developing type 2 diabetes in the Finnish Diabetes Prevention Study (Table 1) (de Mello

Table 1
Metabolic and endocrine impact of diet-derived gut microbiota metabolites during ageing and longevity.

Metabolites	Dietary substrates	Producing microorganisms	Host metabolic and endocrine effects	Changes associated with healthy aging	Changes associated with unhealthy aging	Changes associated with longevity
SCFA: acetate, butyrate, propionate	Carbohydrates (mainly fiber)	*Akkermansia, Bifidobacterium, Butyricimonas, Butyrivibrio, Coprococcus, Eubacterium, Faecalibacterium, Odoribacter, Oscillospira, Prevotella, Roseburia* (Ghosh et al., 2022; Lavelle and Sokol, 2020; O'Toole and Jeffery, 2015; Rampelli et al., 2013; Salazar et al., 2019; Sato et al., 2021)	↑ GLP−1-mediated insulin secretion (Tolhurst et al., 2012); ↑ Gluconeogenesis in enterocytes (De Vadder et al., 2014; Kimura et al., 2013); ↑ YY peptide (Freeland and Wolever, 2010; Larraufie et al., 2018), GLP−1 (Freeland and Wolever, 2010) and leptin (Xiong et al., 2004) secretion (↑ satiety); ↑ Adipose tissue energy expenditure by inducing thermogenesis and fatty acids beta-oxidation (Chambers et al., 2018; Gao et al., 2009; Sahuri-Arisoylu et al., 2016)	↓ SCFA fecal concentrations (Rampelli et al., 2013; Salazar et al., 2019; Sato et al., 2021)	↓↓ Butyrate fecal concentrations associated with frailty (Claesson et al., 2012)	↑ SCFA gut microbiota production and fecal concentrations (Cai et al., 2016; Wu et al., 2019)
Indole and its derivative IPA	L-tryptophan	*Coprococcus*, *Lactobacillus*, *Lactococcus*, *Bacteroides* (Lavelle and Sokol, 2020)	↑ GLP−1-mediated insulin secretion and sensitivity (Chimerel et al., 2014; de Mello et al., 2017)	↓ Indole and IPA gut microbiota production and fecal concentrations (Ruiz-Ruiz et al., 2020)	↓↓ IPA serum concentrations associated with type 2 diabetes (de Mello et al., 2017)	↑ Indole and IPA gut microbiota production (Rampelli et al., 2013)
Imidazole propionate	L-histidine	*Clostridium boltae*, *Ruminococcus gnavus* (Allin et al., 2018; Molinaro et al., 2020; Qin et al., 2012)	↑ Insulin resistance (Fan and Pedersen, 2021; Khan et al., 2014) by impairing insulin receptor substrate signalling in peripheral tissues (Koh et al., 2018)	↑ serum concentrations (Molinaro et al., 2020)	↑↑ serum concentrations associated with pre-diabetes or type 2 diabetes (Molinaro et al., 2020)	Not determined
Metabolites	Dietary substrates	Producing microorganisms	Host metabolic and endocrine effects	Changes associated with healthy aging	Changes associated with unhealthy aging	Changes associated with longevity
Phenols: *p*-cresol, *p*-cresyl sulphate	L-tyrosine	*Clostridium* cluster I and XVI, *Coriobacteriaceae* (Collino et al., 2013; Saito et al., 2018)	↑ Insulin resistance by impairing ERK1/2 signalling pathway in skeletal muscle (rodents) (Koppe et al., 2013)	↑ *p*-cresol fecal concentrations (Claesson et al., 2012; Ghosh et al., 2020a)	↑↑ *p*-cresol fecal concentrations associated with frailty (Claesson et al., 2012; Ghosh et al., 2020a)	↓ *p*-cresol fecal concentrations; ↑ *p*-cresyl sulphate urinary concentrations (Collino et al., 2013; Saito et al., 2018)
Hydrogen sulfide	L-methionine, L-cysteine	*Desulfovibrio*, *Enterobacter*, *Escherichia, Fusobacteria, Klebsiella* (Blachier et al., 2021)	↑ Insulin resistance by stimulating hepatic glucose output (rodents) (Zhang et al., 2013)	Not determined[a]	Not determined[a]	Not determined[a]
Biogenic amines: TMA and TMAO	L-carnitine, choline, phosphatidylcholine	*Escherichia*, *Citrobacter*, *Klebsiella*, *Providentia*, *Shigella* (Cai et al., 2022; Yoshimoto et al., 2021)	↑ Cardiovascular disease risk by promoting atherosclerosis progression (Haghikia et al., 2018; Koeth et al., 2013; Senthong et al., 2016)	↑ TMA fecal concentrations (Yoshimoto et al., 2021); ↑ TMAO serum concentrations (Ke et al., 2018)	↑↑ TMA fecal concentrations associated with frailty (Claesson et al., 2012; Ghosh et al., 2020a)	Not determined

ERK1/2: extracellular signal-regulated kinase 1/2, GLP-1: glucagon-like peptide 1, IPA: indole-3-propionic acid, SCFA: short-chain fatty acids, TMA: trimethylamine, TMAO: trimethylamine N-oxide. Single arrows represent an increase (↑) or a decrease (↓) in metabolic outcomes or metabolite concentrations. Double arrows represent a greater magnitude of effect than a single arrow. aExcluding the hydrogen sulfide of host origin.

et al., 2017).

Compared to young and middle-aged individuals, a reduction in the expression of gut bacterial enzymes involved in the synthesis of indole and its derivatives, as well as a reduction in their fecal concentrations, have been reported in elderly individuals (Ruiz-Ruiz et al., 2020), most probably reflecting the depletion of gut microbiota from their main bacterial producers: the beneficial *Coprococcus* and *Lactobaccillus* (Lavelle and Sokol, 2020). In contrast, a higher capacity of gut bacteria to metabolize tryptophan, and consequently to produce indole and its derivatives, was found in centenarians compared to both elderly (aged between 60 and 75 years old) and young adult individuals (Rampelli et al., 2013). Although fecal concentrations of indole and its derivatives were not measured in these three groups, this result is in agreement with the reduction of tryptophan concentrations found in the serum of centenarians (Table 1) (Collino et al., 2013).

Gut microbiota-derived imidazole propionate (produced from histidine) (Fan and Pedersen, 2021; Khan et al., 2014), phenols (produced from tyrosine) (Canfora et al., 2019; Fan and Pedersen, 2021; Khan et al., 2014; Koppe et al., 2013) and hydrogen sulfide (produced from methionine and cysteine) (Blachier et al., 2021; Canfora et al., 2019; Fan and Pedersen, 2021; Khan et al., 2014; Wu et al., 2009) have been associated with detrimental metabolic and endocrine effects in the host, in particular insulin resistance (Fig. 1 and Table 1). In the case of imidazole propionate, the most well-studied of these metabolites (Fan and Pedersen, 2021; Khan et al., 2014; Koh et al., 2018; Molinaro et al., 2020), Molinaro et al. (2020) observed that in more than 1900 middle-aged and elderly individuals aged between 40 and 67 years old, those who were prediabetic or type 2 diabetic presented higher serum imidazole propionate concentrations compared with those who were heathy. Since dietary intake of histidine was similar in both groups, this

observation likely reflects the greater enrichment in pathobiont bacteria capable of metabolizing histidine to imidazole propionate - such as *C. bolteae* and *Ruminococcus gnavus* - found in the gut microbiota of prediabetic and type 2 diabetic middle-aged and elderly individuals (Allin et al., 2018; Molinaro et al., 2020; Qin et al., 2012). One of the proposed mechanisms by which imidazole propionate contributes to the pathogenesis of type 2 diabetes, is the impairment of the insulin signaling pathway at the level of insulin receptor substrate in liver, skeletal muscle and white adipose tissue cells. This effect is mediated by the activation of p38γ mitogen-activated protein kinase and mechanistic target of rapamycin complex 1 (Koh et al., 2018).

Regarding gut microbiota-derived *p*-cresol, its sulfated metabolite *p*-cresyl sulphate, and hydrogen sulfide, their metabolic and endocrine effects have not been examined in humans yet. However, studies in rodents demonstrated that *p*-cresyl sulphate induces insulin resistance in skeletal muscle cells by activating extracellular signal-regulated kinase 1/2 (ERK1/2) (Koppe et al., 2013). With respect to hydrogen sulfide, this gaseous metabolite increases the risk of hyperglycemia, and consequently of insulin resistance, in mice, by stimulating hepatocyte production of glucose and its release into the blood circulation (Fig. 1) (Zhang et al., 2013). Compared to elderly individuals (aged between 60 and 99 years old), centenarians showed lower fecal concentrations of *p*-cresol (Cai et al., 2016) and higher urinary concentrations of *p*-cresyl sulphate (Collino et al., 2013), suggesting that long-lived individuals may have a greater capacity to metabolize *p*-cresol to *p*-cresyl sulphate and excrete it in urine. On the other hand, elevated fecal levels of *p*-cresol were found to correlate with biomarkers of frailty in elderly individuals (Claesson et al., 2012; Ghosh et al., 2020a), most probably reflecting the greater gut microbiota enrichment in phenols-producing pathobiont bacteria (Ghosh et al., 2022), such as certain *Clostridium* species (Collino et al., 2013; Saito et al., 2018), associated with unhealthy ageing (Table 1) (Ghosh et al., 2022).

The biogenic amine trimethylamine (TMA) is produced from the amino acid L-carnitine or the micronutrient choline - both found in foods of animal origin *e.g.* red meat - by gut bacteria expressing carnitine monooxygenase or TMA lyase, respectively (Cai et al., 2022; Zeisel and Warrier, 2017). After its production, TMA is absorbed through the intestinal epithelium, further oxidized to trimethylamine *N*-oxide (TMAO) in the liver and then released into the blood circulation (Bennett et al., 2013). Elevated plasma levels of TMAO have been positively associated with atherosclerosis progression and, consequently, with an increased risk of developing cardiovascular diseases, such as myocardial infarction and stroke (Table 1) (Haghikia et al., 2018; Senthong et al., 2016). Although not fully elucidated, TMAO's proatherogenic effect seems to be explained by its capacity to inhibit the reverse transport of cholesterol from peripheral tissues and blood circulation to the liver, and to stimulate cholesterol uptake and accumulation in arterial macrophages leading to foam cells formation (Koeth et al., 2013). Furthermore, inhibition of gut microbiota production of TMA and, consequently, its conversion to TMAO by 3,3-dimethyl-1-butanol (a TMA-lyase inhibitor), was found to hamper the development of atherosclerotic lesions in atherosclerosis-prone apolipoprotein E-deficient mice fed a high choline diet (Wang et al., 2015). Even though this inhibitory drug has not yet been evaluated in clinical studies, high plasma levels of TMAO have been proposed as an independent biomarker of atherosclerosis severity (Xie et al., 2021) and cardiovascular risk in humans (Fig. 1) (Tan et al., 2019).

By comparing healthy individuals harboring an adult-type gut microbiota with those harboring an elderly-type one, Yoshimoto et al. (2021) observed an increase in fecal concentrations of TMA in the latter group, most probably reflecting their gut microbiota enrichment in TMA-producing bacteria. In fact, the relative abundance of TMA-producing *Escherichia* and *Klebsiella oxytoca* pathobionts not only was higher in individuals with an elderly-type gut microbiota, but was also found to positively correlate with concentrations of fecal TMA (Yoshimoto et al., 2021). In agreement with these results, plasma concentrations of TMAO were found to be higher in elderly individuals when compared to younger adults (10.5 vs. 2.9 μM) (Ke et al., 2018). These observations strongly suggest that an increase in fecal and blood concentrations of TMA and TMAO, respectively, may in part explain why ageing is an independent risk factor for the development of atherosclerotic cardiovascular diseases (Wang and Bennett, 2012). Moreover, elevated fecal levels of TMA were shown to strongly correlate with biomarkers of frailty in elderly individuals (Claesson et al., 2012; Ghosh et al., 2020a), most probably reflecting the greater gut microbiota enrichment in TMA-producing pathobiont bacteria (Ghosh et al., 2022) associated with unhealthy ageing (Ghosh et al., 2022). To our knowledge, no studies analyzing fecal and serum concentrations of TMA and TMAO, respectively, in centenarians have been published (Table 1). These are undoubtedly necessary to increase the knowledge about the role of these two gut microbiota-derived metabolites in healthy ageing and longevity.

As a whole, evidence presented in Section 4. suggests that healthy aging seems to be associated with a lower gut depletion of beneficial SCFA, indole and IPA, and a lower gut enrichment of detrimental imidazole propionate, phenols and TMA compared to unhealthy aging. In contrast, longevity seems to be associated with a gut enrichment of beneficial SCFA and IPA.

5. Strategies to correct ageing-related changes in gut microbiota

Several interventions have been demonstrated to counteract, at least in part, changes in gut microbiota composition and metabolic function associated with ageing, in particular unhealthy ageing. These interventions aimed to increase the diversity of bacterial species and the abundance of both beneficial and "potentially" beneficial bacteria and their secreted metabolites. Also these intervention aimed to decrease the abundance of pathobiont bacteria and their secreted metabolites (Ghosh et al., 2022) and, simultaneously, improve metabolic outcomes in the ageing host.

Most of the available interventions to counteract gut microbiota changes associated with ageing are dietary-based, since are more easily implemented (DeJong et al., 2020), and include the adherence to the Mediterranean diet and the consumption of specific prebiotic, probiotic and postbiotic supplements (Ghosh et al., 2022). A Mediterranean diet is usually characterized by a high intake of plant-based fiber rich foods such as vegetables, fruits, legumes, whole grain cereals and nuts, and low to moderate intake of animal-based foods such as meat, fish, eggs and dairy products (Guasch-Ferré and Willett, 2021). A study by Ghosh et al. (2020) found that a 1-year adherence to this dietary pattern, consistently altered the fecal microbiota composition of 612 non-frail or pre-frail elderly individuals from five different European countries. The Mediterranean diet attenuated the loss of microbial diversity, increased the abundance of *Faecalibacterium prausnitzii*, *Roseburia*, *Eubacterium*, *Bacteroides thetaiotaomicron* and *Prevotella copri,* and decreased the abundance of *Ruminoccus torques*, *Collinsella aerofaciens*, *Clostridium ramosum* and *Flavonifractor plautii*. These changes, particularly of genera and species whose abundance increased, were positively associated with biomarkers of lower frailty and negatively associated with biomarkers of systemic inflammation (high-sensitivity C-reactive protein and interleukin-17 concentrations). Even though a metabolomic analysis was not performed in this study, an *in silico* prediction based on metagenomic data suggested that the Mediterranean diet promotes SCFA and branched-chain fatty acids production, while decreases phenols (*p*-cresol) and ethanol production (Ghosh et al., 2020b).

Regarding prebiotic supplements, substrates selectively used by specific microorganisms thereby conferring health benefits (Gibson et al., 2017), these include inulin, fructooligosaccharides, galactooligosaccharides and arabinoxylan-oligosaccharides (Ghosh et al., 2022). Probiotic supplements, defined as live microorganisms that when administered in adequate amounts confer health benefits (Hill et al., 2014), include mostly *Lactobacillus* and *Bifidobacteria* species (Ghosh

et al., 2022). With respect to postbiotics - inactivated microorganisms and/or their components, including metabolites, that confer health benefits (Salminen et al., 2021) – they include essentially heat-killed *Lactobacillus* (Ghosh et al., 2022) and *Akkermansia muciniphila* supplements (Depommier et al., 2019). The impact of beneficial microbiota-based metabolites supplementation such as SCFA, indole and its derivatives, whose fecal and blood levels where shown to be decreased during ageing, particularly unhealthy ageing (see Section 4.1. and 4.2.), have not yet been assessed in elderly individuals. This is unexpected since metabolite-based supplements are considered, in general, equally efficacious and safer when compared to probiotic supplements (Sonowal et al., 2017).

On the other hand, non-dietary-based interventions shown to counteract gut microbiota changes associated with ageing include, essentially, fecal microbiota transplant. Despite promising, the feasibility and efficacy of this intervention is not well proven in elderly individuals (Ghosh et al., 2022) due to several constraints. The most challenging ones include: 1) the risk of transmission of pathobionts or pathogenic microorganisms from donors to individuals with a physiological and/or pathological decline of intestinal immune function, as is the case for elderly, 2) engraftment failure of donor microbiota and 3) lack of knowledge regarding individual's own transplantation of feces biobanked during childhood or adolescence (Fan and Pedersen, 2021; Ghosh et al., 2022). Besides fecal microbiota transplant, novel and promising non-dietary-based interventions are being developed such as drugs that inhibit gut microbiota metabolic pathways (*e.g.* enzymes) involved in the synthesis of detrimental metabolites such as TMA (Wang et al., 2015) and *p*-cresol (Harrison et al., 2023), without affecting microorganisms' growth. Considering that clinical studies evaluating the efficacy of both dietary- and non-dietary-based interventions on the gut microbiota profile and metabolic outcomes of elderly individuals have been excellently reviewed elsewhere (Donati Zeppa et al., 2022; Ghosh et al., 2022), they will not be further discussed in this Review. However, an important point that deserves discussion is the individualization or personalization of the above-mentioned microbiota-targeted interventions during ageing. This mainly depends on the pre-intervention gut microbiota profile of elderly individuals, which is determined by several factors such as deterioration of physiological functions, age-related diseases, diet, polypharmacy, genetic background, sex, ethnicity, among others (Ghosh et al., 2022). Therefore, a deep knowledge of the baseline gut microbiota composition (by shotgun metagenomic sequencing) and metabolic function (by metabolomic analysis) and the medical history of elderly individuals, is crucial for selecting the appropriate type of intervention as well as its characteristics (Ghosh et al., 2022).

6. Conclusions

Ageing is associated with profound alterations in gut microbiota composition and metabolic function. One of the most notable ones, is the depletion of beneficial bacteria involved in the metabolism of dietary carbohydrates and aromatic amino acids thereby producing SCFA, indole and IPA - metabolites that exert positive metabolic and endocrine effects in the host. Moreover, ageing is also associated with a notable enrichment in pathobiont bacteria capable of producing imidazole propionate, phenols and amines – metabolites derived from amino acids and other compounds found in foods of animal origin, that exert detrimental metabolic and endocrine effects in the ageing host. Altogether, these changes suggest that the gut microbiota becomes compositionally and functionally less fermentative and more proteolytic during ageing. The magnitude of the above-mentioned changes is much more pronounced in unhealthy than in healthy ageing. However, one particular scenario occurs in longevity, since a distinct gut microbiota signature is displayed by centenarians, the most prominent one being an enrichment in both SCFA and IPA bacterial producers. Regarding the abundance of detrimental metabolites producing-bacteria, it is still unclear if they are decreased or not in these long-lived individuals. Another important knowledge gap is to understand whether changes in gut microbiota profile drive unhealthy or healthy ageing and longevity or, in contrast, age-related changes in host physiological functions and lifestyle patterns (particularly diet) determine gut microbiota composition and metabolic function during ageing. Altought this knowledge gap can be narrowed by performing large and long-term longitudinal human trials, studies using a simple model organism such as the fruit fly, Drosophila melanogaster, demonstrated that changes in microbiota composition may precede aging. Morevover, microbiota modulation of these invertrebrates can extend their lifespan suggesting that microorganisms, and metabolites secreted by them, may predict aging (Broderick and Lemaitre, 2012; Clark et al., 2015).

A considerable number of dietary-based interventions have been demonstrated to counteract ageing-related changes in gut microbiota and improve host metabolic function. To enhance the personalization of these interventions, future studies assessing the impact of novel gut microbiota-derived metabolites, such as those produced from dietary lipids and polyphenols, during healthy or unhealthy ageing are necessary. Finally, metabolites produced by gut virus and fungi should also be subjet of future studies, since recent data demonstrated that the gut microbiota of elderly individuals, particularly of centenarians, is enriched in unique viral and fungal genera (Johansen et al., 2023; Pu et al., 2024).

Funding

Supported by ERDF through the operation POCI-01-0145-ERDF-007746 funded by the Programa Operacional Competitividade e Internacionalização – COMPETE2020 and by FCT - Fundação para a Ciência e a Tecnologia, IP national support through CINTESIS, R&D Unit (UIDB/4255/2020), CHRC (UIDP/04923/2020 and UIDB/04923/2020), and through the projects PTDC/BAA-AGR/7419/2020, 2022.11716.BD and 2020.06333.BD.

Declaration of Competing Interest

None.

Data Availability

No data was used for the research described in the article.

References

Allin, K.H., Tremaroli, V., Caesar, R., Jensen, B.A.H., Damgaard, M.T.F., Bahl, M.I., Licht, T.R., Hansen, T.H., Nielsen, T., Dantoft, T.M., Linneberg, A., Jørgensen, T., Vestergaard, H., Kristiansen, K., Franks, P.W., Hansen, T., Bäckhed, F., Pedersen, O., 2018. Aberrant intestinal microbiota in individuals with prediabetes. Diabetologia 61, 810–820. https://doi.org/10.1007/s00125-018-4550-1.

Barrès, R., Zierath, J.R., 2016. The role of diet and exercise in the transgenerational epigenetic landscape of T2DM. Nat. Rev. Endocrinol. 12, 441–451. https://doi.org/10.1038/nrendo.2016.87.

Bennett, B.J., Vallim, T.Q. de A., Wang, Z., Shih, D.M., Meng, Y., Gregory, J., Allayee, H., Lee, R., Graham, M., Crooke, R., Edwards, P.A., Hazen, S.L., Lusis, A.J., 2013. Trimethylamine-N-Oxide, a metabolite associated with atherosclerosis, exhibits complex genetic and dietary regulation. Cell Metab. 17, 49–60. https://doi.org/10.1016/j.cmet.2012.12.011.

Biagi, E., Franceschi, C., Rampelli, S., Severgnini, M., Ostan, R., Turroni, S., Consolandi, C., Quercia, S., Scurti, M., Monti, D., Capri, M., Brigidi, P., Candela, M., 2016. Gut microbiota and extreme longevity. Curr. Biol. 26, 1480–1485. https://doi.org/10.1016/j.cub.2016.04.016.

Blachier, F., Andriamihaja, M., Larraufie, P., Ahn, E., Lan, A., Kim, E., 2021. Production of hydrogen sulfide by the intestinal microbiota and epithelial cells and consequences for the colonic and rectal mucosa. Am. J. Physiol. Liver Physiol. 320, G125–G135. https://doi.org/10.1152/ajpgi.00261.2020.

Broderick, N.A., Lemaitre, B., 2012. Gut-associated microbes of Drosophila melanogaster. Gut Microbes 3, 307–321. https://doi.org/10.4161/gmic.19896.

Cai, D., Zhao, S., Li, D., Chang, F., Tian, X., Huang, G., Zhu, Z., Liu, D., Dou, X., Li, S., Zhao, M., Li, Q., 2016. Nutrient intake is associated with longevity characterization by metabolites and element profiles of healthy centenarians. Nutrients 8, 564. https://doi.org/10.3390/nu8090564.

Cai, Y.-Y., Huang, F.-Q., Lao, X., Lu, Y., Gao, X., Alolga, R.N., Yin, K., Zhou, X., Wang, Y., Liu, B., Shang, J., Qi, L.-W., Li, J., 2022. Integrated metagenomics identifies a crucial role for trimethylamine-producing Lachnoclostridium in promoting atherosclerosis. NPJ Biofilms Micro 8, 11. https://doi.org/10.1038/s41522-022-00273-4.

Canfora, E.E., Meex, R.C.R., Venema, K., Blaak, E.E., 2019. Gut microbial metabolites in obesity, NAFLD and T2DM. Nat. Rev. Endocrinol. 15, 261–273. https://doi.org/10.1038/s41574-019-0156-z.

Chambers, E.S., Viardot, A., Psichas, A., Morrison, D.J., Murphy, K.G., Zac-Varghese, S.E. K., MacDougall, K., Preston, T., Tedford, C., Finlayson, G.S., Blundell, J.E., Bell, J.D., Thomas, E.L., Mt-Isa, S., Ashby, D., Gibson, G.R., Kolida, S., Dhillo, W.S., Bloom, S. R., Morley, W., Clegg, S., Frost, G., 2015. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. Gut 64, 1744–1754. https://doi.org/10.1136/gutjnl-2014-307913.

Chambers, E.S., Byrne, C.S., Aspey, K., Chen, Y., Khan, S., Morrison, D.J., Frost, G., 2018. Acute oral sodium propionate supplementation raises resting energy expenditure and lipid oxidation in fasted humans. Diabetes Obes. Metab. 20, 1034–1039. https://doi.org/10.1111/dom.13159.

Chimerel, C., Emery, E., Summers, D.K., Keyser, U., Gribble, F.M., Reimann, F., 2014. Bacterial metabolite indole modulates incretin secretion from intestinal enteroendocrine L cells. Cell Rep. 9, 1202–1208. https://doi.org/10.1016/j.celrep.2014.10.032.

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

Clark, R.I., Salazar, A., Yamada, R., Fitz-Gibbon, S., Morselli, M., Alcaraz, J., Rana, A., Rera, M., Pellegrini, M., Ja, W.W., Walker, D.W., 2015. Distinct shifts in microbiota composition during drosophila aging impair intestinal function and drive mortality. Cell Rep. 12, 1656–1667. https://doi.org/10.1016/j.celrep.2015.08.004.

Collino, S., Montoliu, I., Martin, F.-P.J., Scherer, M., Mari, D., Salvioli, S., Bucci, L., Ostan, R., Monti, D., Biagi, E., Brigidi, P., Franceschi, C., Rezzi, S., 2013. Metabolic signatures of extreme longevity in northern italian centenarians reveal a complex remodeling of lipids, amino acids, and gut microbiota metabolism. PLoS One 8, e56564. https://doi.org/10.1371/journal.pone.0056564.

De Vadder, F., Kovatcheva-Datchary, P., Goncalves, D., Vinera, J., Zitoun, C., Duchampt, A., Bäckhed, F., Mithieux, G., 2014. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell 156, 84–96. https://doi.org/10.1016/j.cell.2013.12.016.

DeJong, E.N., Surette, M.G., Bowdish, D.M.E., 2020. The gut microbiota and unhealthy aging: disentangling cause from consequence. Cell Host Microbe 28, 180–189. https://doi.org/10.1016/j.chom.2020.07.013.

Depommier, C., Everard, A., Druart, C., Plovier, H., Van Hul, M., Vieira-Silva, S., Falony, G., Raes, J., Maiter, D., Delzenne, N.M., de Barsy, M., Loumaye, A., Hermans, M.P., Thissen, J.-P., de Vos, W.M., Cani, P.D., 2019. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. Nat. Med. 25, 1096–1103. https://doi.org/10.1038/s41591-019-0495-2.

Donati Zeppa, S., Agostini, D., Ferrini, F., Gervasi, M., Barbieri, E., Bartolacci, A., Piccoli, G., Saltarelli, R., Sestili, P., Stocchi, V., 2022. Interventions on gut microbiota for healthy aging. Cells 12, 34. https://doi.org/10.3390/cells12010034.

Dong, F., Perdew, G.H., 2020. The aryl hydrocarbon receptor as a mediator of host-microbiota interplay. Gut Microbes 12, 1859812. https://doi.org/10.1080/19490976.2020.1859812.

Fan, Y., Pedersen, O., 2021. Gut microbiota in human metabolic health and disease. Nat. Rev. Microbiol. 19, 55–71. https://doi.org/10.1038/s41579-020-0433-9.

Freeland, K.R., Wolever, T.M.S., 2010. Acute effects of intravenous and rectal acetate on glucagon-like peptide-1, peptide YY, ghrelin, adiponectin and tumour necrosis factor-α. Br. J. Nutr. 103, 460–466. https://doi.org/10.1017/S0007114509991863.

Fried, L.P., Cohen, A.A., Xue, Q.-L., Walston, J., Bandeen-Roche, K., Varadhan, R., 2021. The physical frailty syndrome as a transition from homeostatic symphony to cacophony. Nat. Aging 1, 36–46. https://doi.org/10.1038/s43587-020-00017-z.

Frost, G., Sleeth, M.L., Sahuri-Arisoylu, M., Lizarbe, B., Cerdan, S., Brody, L., Anastasovska, J., Ghourab, S., Hankir, M., Zhang, S., Carling, D., Swann, J.R., Gibson, G., Viardot, A., Morrison, D., Louise Thomas, E., Bell, J.D., 2014. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. Nat. Commun. 5, 3611. https://doi.org/10.1038/ncomms4611.

Gao, Z., Yin, J., Zhang, J., Ward, R.E., Martin, R.J., Lefevre, M., Cefalu, W.T., Ye, J., 2009. Butyrate improves insulin sensitivity and increases energy expenditure in mice. Diabetes 58, 1509–1517. https://doi.org/10.2337/db08-1637.

Ghosh, T.S., Das, M., Jeffery, I.B., O'Toole, P.W., 2020a. Adjusting for age improves identification of gut microbiome alterations in multiple diseases. Elife 9, e50240. https://doi.org/10.7554/eLife.50240.

Ghosh, T.S., Rampelli, S., Jeffery, I.B., Santoro, A., Neto, M., Capri, M., Giampieri, E., Jennings, A., Candela, M., Turroni, S., Zoetendal, E.G., Hermes, G.D.A., Elodie, C., Meunier, N., Brugere, C.M., Pujos-Guillot, E., Berendsen, A.M., De Groot, L.C.P.G.M., Feskins, E.J.M., Kaluza, J., Pietruszka, B., Bielak, M.J., Comte, B., Maijo-Ferre, M., Nicoletti, C., De Vos, W.M., Fairweather-Tait, S., Cassidy, A., Brigidi, P., Franceschi, C., O'Toole, P.W., 2020b. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. Gut 69, 1218–1228. https://doi.org/10.1136/gutjnl-2019-319654.

Ghosh, T.S., Shanahan, F., O'Toole, P.W., 2022. The gut microbiome as a modulator of healthy ageing. Nat. Rev. Gastroenterol. Hepatol. 19, 565–584. https://doi.org/10.1038/s41575-022-00605-x.

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

Guasch-Ferré, M., Willett, W.C., 2021. The Mediterranean diet and health: a comprehensive overview. J. Intern. Med. 290, 549–566. https://doi.org/10.1111/joim.13333.

Haghikia, A., Li, X.S., Liman, T.G., Bledau, N., Schmidt, D., Zimmermann, F., Kränkel, N., Widera, C., Sonnenschein, K., Haghikia, A., Weissenborn, K., Fraccarollo, D., Heimesaat, M.M., Bauersachs, J., Wang, Z., Zhu, W., Bavendiek, U., Hazen, S.L., Endres, M., Landmesser, U., 2018. Gut microbiota–dependent trimethylamine N-oxide predicts risk of cardiovascular events in patients with stroke and is related to proinflammatory monocytes. Arterioscler. Thromb. Vasc. Biol. 38, 2225–2235. https://doi.org/10.1161/ATVBAHA.118.311023.

Harrison, M.A., Farthing, R.J., Allen, N., Ahern, L.M., Birchall, K., Bond, M., Kaur, H., Wren, B.W., Bergeron, J.R.C., Dawson, L.F., 2023. Identification of novel p-cresol inhibitors that reduce Clostridioides difficile's ability to compete with species of the gut microbiome. Sci. Rep. 13, 9492. https://doi.org/10.1038/s41598-023-32656-8.

Hill, C., Guarner, F., Reid, G., Gibson, G.R., Merenstein, D.J., Pot, B., Morelli, L., Canani, R.B., Flint, H.J., Salminen, S., Calder, P.C., Sanders, M.E., 2014. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat. Rev. Gastroenterol. Hepatol. 11, 506–514. https://doi.org/10.1038/nrgastro.2014.66.

Hopkins, M.J., 2001. Age and disease related changes in intestinal bacterial populations assessed by cell culture, 16S rRNA abundance, and community cellular fatty acid profiles. Gut 48, 198–205. https://doi.org/10.1136/gut.48.2.198.

Johansen, J., Atarashi, K., Arai, Y., Hirose, N., Sørensen, S.J., Vatanen, T., Knip, M., Honda, K., Xavier, R.J., Rasmussen, S., Plichta, D.R., 2023. Centenarians have a diverse gut virome with the potential to modulate metabolism and promote healthy lifespan. Nat. Microbiol. 8, 1064–1078. https://doi.org/10.1038/s41564-023-01370-6.

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

Khan, M.T., Nieuwdorp, M., Bäckhed, F., 2014. Microbial modulation of insulin sensitivity. Cell Metab. 20, 753–760. https://doi.org/10.1016/j.cmet.2014.07.006.

Kim, B.-S., Choi, C.W., Shin, H., Jin, S.-P., Bae, J.-S., Han, M., Seo, E.Y., Chun, J., Chung, J.H., 2019. Comparison of the gut microbiota of centenarians in longevity villages of south korea with those of other age groups. J. Microbiol. Biotechnol. 29, 429–440. https://doi.org/10.4014/jmb.1811.11023.

Kimura, I., Ozawa, K., Inoue, D., Imamura, T., Kimura, K., Maeda, T., Terasawa, K., Kashihara, D., Hirano, K., Tani, T., Takahashi, T., Miyauchi, S., Shioi, G., Inoue, H., Tsujimoto, G., 2013. The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GPR43. Nat. Commun. 4, 1829. https://doi.org/10.1038/ncomms2852.

Koeth, R.A., Wang, Z., Levison, B.S., Buffa, J.A., Org, E., Sheehy, B.T., Britt, E.B., Fu, X., Wu, Y., Li, L., Smith, J.D., DiDonato, J.A., Chen, J., Li, H., Wu, G.D., Lewis, J.D., Warrier, M., Brown, J.M., Krauss, R.M., Tang, W.H.W., Bushman, F.D., Lusis, A.J., Hazen, S.L., 2013. Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat. Med. 19, 576–585. https://doi.org/10.1038/nm.3145.

Koh, A., Molinaro, A., Ståhlman, M., Khan, M.T., Schmidt, C., Mannerås-Holm, L., Wu, H., Carreras, A., Jeong, H., Olofsson, L.E., Bergh, P.-O., Gerdes, V., Hartstra, A., de Brauw, M., Perkins, R., Nieuwdorp, M., Bergström, G., Bäckhed, F., 2018. Microbially produced imidazole propionate impairs insulin signaling through mTORC1. Cell 175, 947–961.e17. https://doi.org/10.1016/j.cell.2018.09.055.

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

Kong, F., Deng, F., Li, Y., Zhao, J., 2019. Identification of gut microbiome signatures associated with longevity provides a promising modulation target for healthy aging. Gut Microbes 10, 210–215. https://doi.org/10.1080/19490976.2018.1494102.

Koppe, L., Pillon, N.J., Vella, R.E., Croze, M.L., Pelletier, C.C., Chambert, S., Massy, Z., Glorieux, G., Vanholder, R., Dugenet, Y., Soula, H.A., Fouque, D., Soulage, C.O., 2013. p-cresyl sulfate promotes insulin resistance associated with CKD. J. Am. Soc. Nephrol. 24, 88–99. https://doi.org/10.1681/ASN.2012050503.

Larraufie, P., Martin-Gallausiaux, C., Lapaque, N., Dore, J., Gribble, F.M., Reimann, F., Blottiere, H.M., 2018. SCFAs strongly stimulate PYY production in human enteroendocrine cells. Sci. Rep. 8, 74. https://doi.org/10.1038/s41598-017-18259-0.

Lavelle, A., Sokol, H., 2020. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. Nat. Rev. Gastroenterol. Hepatol. 17, 223–237. https://doi.org/10.1038/s41575-019-0258-z.

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

López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2023. Hallmarks of aging: an expanding universe. Cell 186, 243–278. https://doi.org/10.1016/j.cell.2022.11.001.

de Mello, V.D., Paananen, J., Lindström, J., Lankinen, M.A., Shi, L., Kuusisto, J., Pihlajamäki, J., Auriola, S., Lehtonen, M., Rolandsson, O., Bergdahl, I.A., Nordin, E., Ilanne-Parikka, P., Keinänen-Kiukaanniemi, S., Landberg, R., Eriksson, J.G., Tuomilehto, J., Hanhineva, K., Uusitupa, M., 2017. Indolepropionic acid and novel lipid metabolites are associated with a lower risk of type 2 diabetes in the Finnish Diabetes Prevention Study. Sci. Rep. 7, 46337 https://doi.org/10.1038/srep46337.

Molinaro, A., Bel Lassen, P., Henricsson, M., Wu, H., Adriouch, S., Belda, E., Chakaroun, R., Nielsen, T., Bergh, P.-O., Rouault, C., André, S., Marquet, F., Andreelli, F., Salem, J.-E., Assmann, K., Bastard, J.-P., Forslund, S., Le Chatelier, E., Falony, G., Pons, N., Prifti, E., Quinquis, B., Roume, H., Vieira-Silva, S., Hansen, T. H., Pedersen, H.K., Lewinter, C., Sønderskov, N.B., Alves, R., Amouyal, C., Galijatovic, E.A.A., Barthelemy, O., Batisse, J.-P., Berland, M., Bittar, R., Blottière, H., Bosquet, F., Boubrit, R., Bourron, O., Camus, M., Cassuto, D., Chilloux, J., Ciangura, C., Coelho, L.P., Collet, J.-P., Dao, M.-C., Djebbar, M., Doré, A., Engelbrechtsen, L., Fellahi, S., Fezeu, L., Fromentin, S., Giral, P., Gøtze, J. P., Hartemann, A., Holst, J.J., Hercberg, S., Helft, G., Hornbak, M., Hulot, J.-S., Isnard, R., Jaqueminet, S., Jørgensen, N.R., Julienne, H., Justesen, J., Kammer, J., Krarup, N., Kerneis, M., Khemis, J., Kristensen, N.B., Kuhn, M., Lejard, V., Levenez, F., Lucas-Martini, L., Massey, R., Maziers, N., Medina-Stamminger, J., Montalescot, G., Moutel, S., Le Pavin, L.P., Poitou, C., Pousset, F., Pouzoulet, L., Schmidt, S., Moitinho-Silva, L., Silvain, J., Sokolovska, N., Touch, S., Svendstrup, M., Swartz, T., Vanduyvenboden, T., Vatier, C., Walther, S., Køber, L., Vestergaard, H., Hansen, T., Zucker, J.-D., Galan, P., Dumas, M.-E., Raes, J., Oppert, J.-M., Letunic, I., Nielsen, J., Bork, P., Ehrlich, S.D., Stumvoll, M., Pedersen, O., Aron-Wisnewsky, J., Clément, K., Bäckhed, F., 2020. Imidazole propionate is increased in diabetes and associated with dietary patterns and altered microbial ecology. Nat. Commun. 11, 5881. https://doi.org/10.1038/s41467-020-19589-w.

O'Toole, P.W., Jeffery, I.B., 2015. Gut microbiota and aging. Science 350, 1214–1215. https://doi.org/10.1126/science.aac8469.

Pu, L., Pang, S., Mu, W., Chen, X., Zou, Y., Wang, Y., Ding, Y., Yan, Q., Huang, Y., Chen, X., Peng, T., Luo, W., Wang, S., 2024. The gut mycobiome signatures in long-lived populations. iScience, 110412. https://doi.org/10.1016/j.isci.2024.110412.

Qin, J., Li, Y., Cai, Z., Li, S., Zhu, J., Zhang, F., Liang, S., Zhang, W., Guan, Y., Shen, D., Peng, Y., Zhang, D., Jie, Z., Wu, W., Qin, Y., Xue, W., Li, J., Han, L., Lu, D., Wu, P., Dai, Y., Sun, X., Li, Z., Tang, A., Zhong, S., Li, X., Chen, W., Xu, R., Wang, M., Feng, Q., Gong, M., Yu, J., Zhang, Y., Zhang, M., Hansen, T., Sanchez, G., Raes, J., Falony, G., Okuda, S., Almeida, M., LeChatelier, E., Renault, P., Pons, N., Batto, J.-M., Zhang, Z., Chen, H., Yang, R., Zheng, W., Li, S., Yang, H., Wang, J., Ehrlich, S.D., Nielsen, R., Pedersen, O., Kristiansen, K., Wang, J., 2012. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 490, 55–60. https://doi.org/10.1038/nature11450.

Rampelli, S., Candela, M., Turroni, S., Biagi, E., Collino, S., Franceschi, C., O'Toole, P.W., Brigidi, P., 2013. Functional metagenomic profiling of intestinal microbiome in extreme ageing. Aging 5, 902–912. https://doi.org/10.18632/aging.100623.

Rowe, J.W., Kahn, R.L., 1987. Human aging: usual and successful. Science 237, 143–149. https://doi.org/10.1126/science.3299702.

Ruiz-Ruiz, S., Sanchez-Carrillo, S., Ciordia, S., Mena, M.C., Méndez-García, C., Rojo, D., Bargiela, R., Zubeldia-Varela, E., Martínez-Martínez, M., Barbas, C., Ferrer, M., Moya, A., 2020. Functional microbiome deficits associated with ageing: chronological age threshold. Aging Cell 19, e13063. https://doi.org/10.1111/acel.13063.

Sahuri-Arisoylu, M., Brody, L.P., Parkinson, J.R., Parkes, H., Navaratnam, N., Miller, A. D., Thomas, E.L., Frost, G., Bell, J.D., 2016. Reprogramming of hepatic fat accumulation and "browning" of adipose tissue by the short-chain fatty acid acetate. Int. J. Obes. 40, 955–963. https://doi.org/10.1038/ijo.2016.23.

Saito, Y., Sato, T., Nomoto, K., Tsuji, H., 2018. Identification of phenol- and p-cresol-producing intestinal bacteria by using media supplemented with tyrosine and its metabolites. FEMS Microbiol. Ecol. 94, fiy125 https://doi.org/10.1093/femsec/fiy125.

Salazar, N., Arboleya, S., Fernández-Navarro, T., de los Reyes-Gavilán, C.G., Gonzalez, S., Gueimonde, M., 2019. Age-associated changes in gut microbiota and dietary components related with the immune system in adulthood and old age: a cross-sectional study. Nutrients 11, 1765. https://doi.org/10.3390/nu11081765.

Salminen, S., Collado, M.C., Endo, A., Hill, C., Lebeer, S., Quigley, E.M.M., Sanders, M.E., Shamir, R., Swann, J.R., Szajewska, H., Vinderola, G., 2021. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. Nat. Rev. Gastroenterol. Hepatol. 18, 649–667. https://doi.org/10.1038/s41575-021-00440-6.

Sato, Y., Atarashi, K., Plichta, D.R., Arai, Y., Sasajima, S., Kearney, S.M., Suda, W., Takeshita, K., Sasaki, T., Okamoto, S., Skelly, A.N., Okamura, Y., Vlamakis, H., Li, Y., Tanoue, T., Takei, H., Nittono, H., Narushima, S., Irie, J., Itoh, H., Moriya, K., Sugiura, Y., Suematsu, M., Moritoki, N., Shibata, S., Littman, D.R., Fischbach, M.A., Uwamino, Y., Inoue, T., Honda, A., Hattori, M., Murai, T., Xavier, R.J., Hirose, N., Honda, K., 2021. Novel bile acid biosynthetic pathways are enriched in the microbiome of centenarians. Nature 599, 458–464. https://doi.org/10.1038/s41586-021-03832-5.

Senthong, V., Wang, Z., Li, X.S., Fan, Y., Wu, Y., Wilson Tang, W.H., Hazen, S.L., 2016. Intestinal microbiota-generated metabolite trimethylamine-N-oxide and 5-year mortality risk in stable coronary artery disease: the contributory role of intestinal microbiota in a COURAGE-like patient cohort. J. Am. Heart Assoc. 5, e002816 https://doi.org/10.1161/JAHA.115.002816.

Sonowal, R., Swimm, A., Sahoo, A., Luo, L., Matsunaga, Y., Wu, Z., Bhingarde, J.A., Ejzak, E.A., Ranawade, A., Qadota, H., Powell, D.N., Capaldo, C.T., Flacker, J.M., Jones, R.M., Benian, G.M., Kalman, D., 2017. Indoles from commensal bacteria extend healthspan. Proc. Natl. Acad. Sci. 114, E7506–E7515. https://doi.org/10.1073/pnas.1706464114.

Tan, Y., Sheng, Z., Zhou, P., Liu, C., Zhao, H., Song, L., Li, J., Zhou, J., Chen, Y., Wang, L., Qian, H., Sun, Z., Qiao, S., Xu, B., Gao, R., Yan, H., 2019. Plasma trimethylamine N-oxide as a novel biomarker for plaque rupture in patients with ST-segment–elevation myocardial infarction. Circ. Cardiovasc. Interv. 12, e007281 https://doi.org/10.1161/CIRCINTERVENTIONS.118.007281.

Tolhurst, G., Heffron, H., Lam, Y.S., Parker, H.E., Habib, A.M., Diakogiannaki, E., Cameron, J., Grosse, J., Reimann, F., Gribble, F.M., 2012. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein–coupled receptor FFAR2. Diabetes 61, 364–371. https://doi.org/10.2337/db11-1019.

Tuikhar, N., Keisam, S., Labala, R.K., Ramakrishnan, I.P., Arunkumar, M.C., Ahmed, G., Biagi, E., Jeyaram, K., 2019. Comparative analysis of the gut microbiota in centenarians and young adults shows a common signature across genotypically non-related populations. Mech. Ageing Dev. 179, 23–35. https://doi.org/10.1016/j.mad.2019.02.001.

United Nations, 2019. World Population Ageing 2019: Highlights (ST/ESA/SER.A/430). https://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2019-Report.pdf (accessed 9 July 2024).

Wang, J.C., Bennett, M., 2012. Aging and atherosclerosis. Circ. Res. 111, 245–259. https://doi.org/10.1161/CIRCRESAHA.111.261388.

Wang, Z., Roberts, A.B., Buffa, J.A., Levison, B.S., Zhu, W., Org, E., Gu, X., Huang, Y., Zamanian-Daryoush, M., Culley, M.K., DiDonato, A.J., Fu, X., Hazen, J.E., Krajcik, D., DiDonato, J.A., Lusis, A.J., Hazen, S.L., 2015. Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. Cell 163, 1585–1595. https://doi.org/10.1016/j.cell.2015.11.055.

Wilmanski, T., Diener, C., Rappaport, N., Patwardhan, S., Wiedrick, J., Lapidus, J., Earls, J.C., Zimmer, A., Glusman, G., Robinson, M., Yurkovich, J.T., Kado, D.M., Cauley, J.A., Zmuda, J., Lane, N.E., Magis, A.T., Lovejoy, J.C., Hood, L., Gibbons, S. M., Orwoll, E.S., Price, N.D., 2021. Gut microbiome pattern reflects healthy ageing and predicts survival in humans. Nat. Metab. 3, 274–286. https://doi.org/10.1038/s42255-021-00348-0.

Wu, L., Yang, W., Jia, X., Yang, G., Duridanova, D., Cao, K., Wang, R., 2009. Pancreatic islet overproduction of H2S and suppressed insulin release in Zucker diabetic rats. Lab. Investig. 89, 59–67. https://doi.org/10.1038/labinvest.2008.109.

Wu, L., Zeng, T., Zinellu, A., Rubino, S., Kelvin, D.J., Carru, C., 2019. A Cross-sectional study of compositional and functional profiles of gut microbiota in sardinian centenarians. mSystems 4, e00325-19. https://doi.org/10.1128/mSystems.00325-19.

Xie, G., Yan, A., Lin, P., Wang, Y., Guo, L., 2021. Trimethylamine N-oxide—a marker for atherosclerotic vascular disease. Rev. Cardiovasc. Med. 22, 787. https://doi.org/10.31083/j.rcm2203085.

Xiong, Y., Miyamoto, N., Shibata, K., Valasek, M.A., Motoike, T., Kedzierski, R.M., Yanagisawa, M., 2004. Short-chain fatty acids stimulate leptin production in adipocytes through the G protein-coupled receptor GPR41. Proc. Natl. Acad. Sci. 101, 1045–1050. https://doi.org/10.1073/pnas.2637002100.

Yoshimoto, S., Mitsuyama, E., Yoshida, K., Odamaki, T., Xiao, J., 2021. Enriched metabolites that potentially promote age-associated diseases in subjects with an elderly-type gut microbiota. Gut Microbes 13, 1–11. https://doi.org/10.1080/19490976.2020.1865705.

Zeisel, S.H., Warrier, M., 2017. Trimethylamine N-oxide, the microbiome, and heart and kidney disease. Annu. Rev. Nutr. 37, 157–181. https://doi.org/10.1146/annurev-nutr-071816-064732.

Zhang, L., Yang, G., Untereiner, A., Ju, Y., Wu, L., Wang, R., 2013. Hydrogen sulfide impairs glucose utilization and increases gluconeogenesis in hepatocytes. Endocrinology 154, 114–126. https://doi.org/10.1210/en.2012-1658.

Zhang, X., Zhong, H., Li, Y., Shi, Z., Ren, H., Zhang, Z., Zhou, X., Tang, S., Han, X., Lin, Y., Yang, F., Wang, D., Fang, C., Fu, Z., Wang, L., Zhu, S., Hou, Y., Xu, X., Yang, H., Wang, J., Kristiansen, K., Li, J., Ji, L., 2021. Sex- and age-related trajectories of the adult human gut microbiota shared across populations of different ethnicities. Nat. Aging 1, 87–100. https://doi.org/10.1038/s43587-020-00014-2.