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The role of a Mediterranean diet and physical activity in decreasing age-related inflammation through modulation of the gut microbiota composition

Jessie S. Clark[1,2], Bradley S. Simpson[1] and Karen J. Murphy[1,2]*

[1]*University of South Australia, Clinical and Health Sciences, GPO Box 2471, Adelaide 5001, Australia*
[2]*Alliance for Research in Exercise, Nutrition and Activity, University of South Australia, GPO Box 2471, Adelaide 5001, Australia*

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Abstract

Chronic inflammation is known to be a predominant factor in the development of many age-related conditions including CVD, type II diabetes and neurodegenerative diseases. Previous studies have demonstrated that during the ageing process there is an increase in inflammatory biomarkers, which may be partially brought about by detrimental changes in the gut microbiota. The Mediterranean diet (MedDiet) and physical activity (PA) are protective against inflammation and chronic disease, and emerging evidence has shown that these effects may be partially mediated through favourable changes in the gut microbiota. In this review, we have evaluated the published literature on the effect of a MedDiet and PA on the gut microbiota. We also discuss the relationship between the gut microbiota and inflammation with a focus on healthy ageing. While inconsistent study designs make forming definitive conclusions challenging, the current evidence suggests that both a MedDiet and PA are capable of modifying the gut microbiota in a way that is beneficial to host health. For example, the increases in the relative abundance of SCFA producing bacteria that are considered to possess anti-inflammatory properties. Modification of the gut microbiota through a MedDiet and PA presents as a potential method to attenuate age-related increases in inflammation, and additional studies utilising older individuals are needed to fill the knowledge gaps existing in current literature.

Key words: **Mediterranean diet: Gut microbiota: Inflammation: Physical activity**

With current projections placing 1·5 billion people globally over the age of 65 by the year 2050, it has never been more important to identify strategies that promote the maintenance of health, well-being and functionality through a person's older years. Chronic inflammation has been identified as a predominant factor contributing to the onset and progression of many age-related diseases[1]. The acute inflammatory response is an essential function of a healthy immune system that is triggered in response to chemical or physical stimuli. This process is tightly regulated as inadequate resolution of inflammation or a prolonged exposure to the inflammatory trigger may lead to a state of chronic inflammation that may contribute to the aetiology of diseases such as cancers, type 2 diabetes, atherosclerosis and cardiovascular and neurodegenerative diseases[2,3].

As humans age, there is a notable dysregulation of the immune system which involves a marked decline in the adaptive responses and mild increases in innate activity. This process, called immunosenescence, can impair a person's ability to fight infection, weaken vaccination response and lead to higher levels of adiposity, and changes in the gut microbiota composition. These outcomes can lead to a state of chronic low-grade inflammation termed inflammageing[4]. This immune dysregulation is accompanied by increased levels of pro-inflammatory cytokines, such as IL-6, TNF-α and C-reactive protein, particularly in older people[5,6]. Increased inflammation, specifically levels of C-reactive protein, IL-6 and TNF-α, has been associated with many age-related diseases including sarcopenia, osteoporosis and fracture, malnutrition, cognitive decline, increased risk of frailty and increased all-cause mortality[1,7].

There are many common lifestyle factors that can contribute to chronic inflammation, for instance smoking, alcohol consumption, chronic stress and importantly, poor diet and lack of physical activity (PA). The Mediterranean Diet (MedDiet), a centuries-old dietary pattern evolving from the traditional eating patterns of the countries surrounding the Mediterranean basin, has long been touted as one of the most favourable dietary patterns for promoting good health and longevity[8]. The diet is predominantly plant based containing high amounts of fruits and vegetables, extra virgin olive oil (EVOO), wholegrains and

Abbreviations: EVOO, extra virgin olive oil; MedDiet, Mediterranean diet; PA, physical activity.

* **Corresponding author:** Karen J. Murphy, email karen.murphy@unisa.edu.au

legumes with moderate consumption of poultry, dairy foods and wine, and low intakes of discretionary foods and red and processed meats[9]. Early research by Ancel Keys and the Seven Countries Study highlighted the protective effect of the MedDiet against CVD[10,11], and follow-up studies have continued to show the protective effects of a MedDiet across a range of other chronic diseases and overall mortality[12,13]. While this strong evidence exists, some mechanisms supporting these outcomes are not completely understood. One proposed mechanism of action is via the gut microbiota and the reduction of chronic inflammation, a state which underpins many chronic diseases[14,15].

The aim of this narrative review is to provide an overview of the MedDiet diet and lifestyle, summarise the current evidence on how both a MedDiet and PA influence the human gut microbiota and discuss the relationship between the gut microbiota and healthy ageing, with a focus on inflammation.

Mediterranean diet and lifestyle

The MedDiet has existed for centuries, evolving from the traditional eating patterns of people native to countries surrounding the Mediterranean basin. It is not just one pattern, but rather numerous variations of a similar way of eating, determined by local food availability and cultural and religious practices[16]. Despite these differences, the region's dietary pattern consists of the same core principles and a focus on fresh wholefoods with limited processing. The diet is predominantly plant based with high intakes of fruits and vegetables, wholegrains, legumes, nuts and seeds and includes a moderate to high consumption of high-quality dietary fats, primarily from EVOO. There is a preference for fish over red meat, limited sweets and a moderate consumption of red wine around mealtimes and social settings[9]. However, the MedDiet is more than just the food consumed in these regions; the dietary pattern is heavily underpinned with physical activity, adequate rest, culinary activities, frugality and a high degree of socialisation and community[17].

Research focusing on the MedDiet began in the 1950s when Ancel Keys and the team of the Seven Countries Study investigated the relationship between CVD and various lifestyle factors after noticing the differences in CVD between American businessmen and those living in post-war Europe[10]. Multiple follow-up studies have demonstrated the association between dietary patterns, like those seen in the cohorts from Italy and Greece, and a reduced risk of CHD[10,11]. Interest in the MedDiet's effects on health outcomes has only grown in the past few decades. A recent umbrella review by Dinu *et al.*[18] meta-analysed sixteen randomised controlled trials and thirteen meta-analyses of observational studies, involving 12·8 million participants, investigating the relationship between the adherence to a MedDiet and health outcomes. The review provides strong evidence for the protective nature of the MedDiet with an 11 % reduced risk in overall mortality (95 % CI 0·89, 0·93), 33 % reduced risk of CVD (95 % CI 0·58, 0·77) and a 21 % reduced risk of neurodegenerative diseases (95 % CI 0·70, 0·90)[18]. An increasing number of studies are also focusing on the MedDiet's impact in maintaining the physical functioning of older people demonstrating an association between higher adherence to a MedDiet and reduced risk of frailty, sarcopenia and development of a mobility disabilities and increased skeletal muscle retention and handgrip strength[19–21].

Traditionally, the populations of the Mediterranean region had high incidental levels of PA due to the laborious nature of their occupational status. For instance, in 1960's Crete, many inhabitants were shepherds or farmers who would travel up to 20 and 8 km on foot per day, respectively, often on uneven or rugged terrain[22]. This is a stark contrast to the current lifestyles of those living in developed nations where sedentary behaviours have been increasing for decades due to technological advances and the rise of less active occupations[23]. The health benefits of PA are widely accepted in the literature, and it has been associated with reducing the risk of premature mortality and multiple chronic health conditions including some forms of cancer, CVD, metabolic conditions and risk of stroke[24].

Human gut microbiota through life

The gut microbiota consists of approximately 100 trillion microbial cells that form a symbiotic relationship with its human host, exerting many beneficial physiological effects that are protective of disease including maintaining the integrity of the intestinal epithelium, energy extraction from undigestible material, prevention of colonisation by pathogenic microbes and involvement in immune system development and regulation[25,26]. It is comprised of several bacterial phyla, with Firmicutes and Bacteroidetes being identified as the two most dominant. The relative abundance of these two phyla appears to be an important determinant of human health[26]. However, many members of these phyla are capable of exerting different effects through the individual genes they carry, and therefore their ability to produce metabolites like SCFA and bioactive compounds[27], suggesting that microbiota diversity and relative abundance of particular taxa, along with their functional capability, may be more important[28].

Microbiota colonisation begins at birth and continues to transform rapidly during the early years of life, stabilising at approximately 2–5 years of age where its composition resembles that of an adult microbiota[29]. From this point, the stability and resilience of an individual's core microbiota increase and temporary external factors, like short-term dietary changes or the use of antibiotics, generate only transient changes in composition. As humans age, there is a gradual and continual shift in lifestyle that includes decreases in nutritional quality and PA, increased intestinal transit time and higher use of medications, which produce a compounding effect on the gut microbiota, and composition begins to alter[30]. These alterations present as a loss of microbial diversity, increased inter-individual variability and shifts in the relative abundance of numerous species[31,32]. Specific changes that have been reported are decreases in Clostridium cluster IV, *Faecalibacterium prausnitzii* and bifidobacterial members, which are all known for their ability to produce SCFA through the fermentation of fibre[31,33–35]. One of the largest studies conducted in an elderly cohort analysed the microbiota composition of participants who were living in different circumstances/environments. The authors reported significant decreases in

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the microbiota diversity of the elderly participants in long-stay care compared with that of community-dwelling participants, and that this loss of diversity was significantly associated with an increase in frailty. Further investigation found the microbiota shift found in these populations was primarily driven by dietary intake[28]. Recently, research has investigated the microbiota composition on centenarians, individuals who demonstrate healthy ageing and longevity. Numerous studies have reported a decrease in the core taxa and increases in sub-dominant species including opportunistic pathogens and usually transient bacteria including *Methanobrevibacter* and *Escherichia*[36,37]. Similar to elderly cohorts, decreases in the relative abundance of SCFA producing *Faecalibacterium* have been reported in centenarians; however, the relative abundance of health promoting bacteria *Akkermansia*, *Bifidobacterium* and *Christensellaceae* is also commonly reported, perhaps promoting health benefits through functional redundancy[37,38]. Wu *et al.* also reported that the functional profile of a centenarian gut microbiota was distinctly different than that of elderly and young adult participants, including increased SCFA pathways and altered amino acid metabolism[36]. Similar shifts in taxonomic and functional profiles were reported in a 2021 study in an elderly population[39]. The authors reported an increasingly unique microbiota composition with age, with a decrease in the relative abundance of Bacteroides, and increases in *Christensellaceae, Methanobrevibacter* and *Desulfibrio* in healthy participants, with these changes correlating with a decreased risk of mortality in participants over 85 years of age. Further, genus level uniqueness was associated with altered amino acid metabolism, with increases in phenylalanine/tyrosine and tryptophan metabolism[39]. Unfortunately, the cross-sectional nature of studies investigating the gut microbiota of elderly individuals and centenarians makes it impossible to ascertain if the certain taxa seen in healthy ageing are present in the earlier years of life and contribute to the longevity observed, or if the microbiota itself is a consequence of reaching extreme ageing.

Dietary intake and the gut microbiota

As research into the gut microbiota has developed, it has been widely accepted that an individual's diet and lifestyle is one of the strongest modifiable factors that influences microbial richness, diversity and composition[40,41]. The influence of diet has been studied over the past two decades, providing an understanding of how nutrition can promote the growth of certain microbial taxa by providing their preferred substrate, but many studies have focused on particular foods or select nutrients[42,43]. There is an abundance of research identifying dietary fibre as a key modifier of gut microbiota composition by increasing the relative abundance of beneficial SCFA producers[43]. As research continues to strengthen the role of the microbiota in host health and disease, additional foods and food components have begun to be investigated. Dietary fats have become of interest due to their ability to traverse the large intestine and colon intact, where they are metabolised by the local gut bacteria and potentially influence microbial composition. Until recently, the effects of high dietary fat intakes on the gut microbiota have failed to differentiate between the fatty acid profiles of meat-based Westernised diets and a plant-centred diet like the MedDiet, which includes high intakes of EVOO, *n*-3 fatty acids and nuts. While human studies have been scarce thus far, there is emerging evidence that due to its high concentration of phenolic compounds, EVOO can exert both prebiotic and antibacterial effects on the gut microbiota, resulting in increases in beneficial *Lactobacillus* and *Bifidobacterium* and decreases in the potentially pathogenic *Staphylococcus*[44–46]. Recent intervention studies have also highlighted the beneficial impacts of *n*-3 fatty acids on the gut microbiota, showing that they are capable of increasing the relative abundance of SCFA producers in a similar fashion to that of fibre[47,48]. Further, multiple studies investigating the effect of nuts on the gut microbiota have shown that almonds, pistachios and walnuts are all capable of exerting effects on the relative abundance of various gut bacteria. While differences in fatty acid composition between the three types of nuts present difficulties in providing conclusive results, the intake of high PUFA containing walnuts produced significant shifts in β-diversity in all three studies[49–51]. Additional foods that constitute a MedDiet that have been shown to modulate gut microbiota are dairy foods like milk and yogurt, and polyphenol-rich fruits, vegetables and red wine[52–55]. A sample of studies detailing the impacts of these foods on the gut microbiota can be found in Table 1.

Recently, there has been a shift towards investigating the role that whole dietary patterns and other lifestyle factors, including PA, play in establishing and modifying the human microbiota. So far, a number of studies have shown PA to be a novel influencer of microbiota composition; however, the mechanisms are not well understood[56].

Effects of a Mediterranean diet and lifestyle on the gut microbiota

Research into the effect of a MedDiet and the microbiota is still in its infancy, with only a limited amount studies being published in the last 5 years. With its emphasis on wholegrains, fruits, vegetables and legumes, the MedDiet is an excellent source of complex carbohydrates and non-digestible fibre, preferentially used by certain microbes as a substrate to produce SCFA (e.g. butyrate) that are beneficial to host health[57]. In one of the earliest studies, De Filippis *et al.* compared the habitual diet of Italian vegans, vegetarians and omnivores regarding their MedDiet adherence and microbiota composition. While they found no significant difference in diversity across diet groups or adherence levels, those who showed higher adherence to a MedDiet reported higher levels of faecal SCFA[58]. The relationship between MedDiet adherence and faecal SCFA has been corroborated in three subsequent cohort studies where researchers also found changes in the relative abundance of certain microbes[59–61]. These changes included an increase in *F. prausnitzii,* a known butyrate producer considered to have anti-inflammatory properties[62], and lower levels of *Escherichia coli,* a well-known gut coloniser with pathogenic and inflammatory potential[63].

A recent observational study by Gallè and colleagues collected the habitual dietary habits, PA levels and microbiota composition of 140 Italian university students. A higher adherence to a MedDiet was associated with higher relative abundance of

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Table 1. Summary of studies assessing the impact of Mediterranean diet component and a whole Mediterranean diet intervention on the human gut microbiota

	Study	Design	Participants	Intervention/details	Impact on gut microbiota composition
n-3					
Mixed (EPA) and (DHA)	Watson *et al.*[114]	Randomised cross-over study	22 healthy adults (> 50 years of age)	8-week treatment phase of 4 g mixed EPA/DHA in a soft-gel capsule or a Smartfish liquid formula drink. Each intervention was separated by a 12-week washout period	Increased relative abundance of several taxa including Roseburia, Bifidobacterium, Lachnospira and *Oscillospira*. Significant increased relative abundance of *Roseburia* in the Smartfish drink portion of the trial
Mixed (EPA) and (DHA)	Vijay *et al.*[49]	Randomised parallel-arm intervention study	72 healthy adults with a BMI 20–39·9 kg/m^2	Participants were randomised into two interventions: 20 g inulin fibre (*n* 35) and 500 mg of a mixed *n*-3 supplement (*n* 37) daily for 6 weeks	Significant increase in the relative abundance of *Coprococcus* and *Bacteroides* in the *n*-3 group
Sardines	Balfego *et al.*[115]	Randomised pilot intervention study	35 drug naïve patient with type II diabetes BMI 26–35 kg/m^2	Participants were randomised to follow either a standard diabetes diet (control group (*n* 16)) or the standard diabetes diet supplemented with 100 g of sardines (sardine groups (*n* 19)), 5 times per week for 6 months	A significant decrease in *Bacteroidetes* was reported in both groups. Significant increase in the relative abundance of the *Bacteroides-Prevotella* group in the sardine group
Serum *n*-3 fatty acids	Menni *et al.*[116]	Cross-sectional study	876 female participants from the UK Twins Registry	Serum *n*-3 fatty acids and gut microbiota samples were used	Serum *n*-3 was positively associated with gut microbiota diversity. Serum DHA levels were strongly correlated with members of the *Lachnospiraceae* family
Fish protein	Noriega *et al.*[117]	Case report	45-year-old healthy male (*n* 1)	600 mg of *n*-3 daily (from fish) for 2 weeks	Increase in the Bacteroidetes phylum. Increases in *Blautia, Coprococcus, Roseburia, Ruminococcus* and *Subdoligranulum* genera. Decrease in *Faecalibacterium*
Nuts					
Almonds	Dhillon *et al.*[118]	Randomised, controlled parallel-arm intervention study	73 college students aged 18–19 years with a BMI 18–41 kg/m^2	Students were randomly assigned one of two interventions; and almond snacking group who consumed 57 g of almonds daily (*n* 38) or the cracker snacking group who consumed 77·5 g of Graham crackers daily (*n* 35), for 8 weeks	The almond snacking group had a significant increase in α-diversity and a significant decrease in the relative abundance of *Bacteroides fragilis*
Almonds	Burns *et al.*[119]	Randomised, controlled cross-over study	29 parents (18–40 years of age) with at least 1 child, recruited as pairs	Parent–child pairs were randomly allocated into the almond intervention (1·5 oz and 0·5 oz of whole almonds or almond butter for parent and child, respectively) or the control intervention (no almonds) for 3 weeks before alternating to the other intervention after a 6-week washout period	No significant differences in diversity or composition were reported between each intervention stage
Almonds OR Pistachios	Ukhanova *et al.*[120]	2 Randomised, controlled cross-over study	Healthy adult participants. Almond study (*n* 18). Pistachio study (*n* 16)	In both studies, participants were randomised to 3, 18-d intervention periods separated by a 2-week washout Phase 1 – 0 g of nuts. Phase 2 – 42 g of nuts. Phase 3 – 84 g of nuts	Significant decrease in the relative abundance of lactic acids bacteria following pistachio consumption
Walnuts	Holscher *et al.*[52]	Randomised cross-over study	Healthy adults with a BMI 20–38 kg/m^2	Participants were randomly assigned to isoenergetic diets that contained either 42 g or 0 g of walnuts daily for 3 weeks, then swapped to the other intervention after a 1-week washout period	Significantly increased relative abundance of *Faecalibacterium, Clostridium Dialster* and *Roseburia*, and significantly decreased relative abundance of Bifidobacterium, *Ruminococcus, Dorea* and *Oscillospira*
Walnuts	Bamberger *et al.*[50]	Randomised, controlled cross-over study	135 healthy adults > 50 years of age	After a 4 week Western-style diet run in, participants were randomised into two different diet phases, both lasting 8 weeks, before switching to the other diet after a 4-week washout period. One diet was a control diet enriched with 43 g of walnuts daily (WG), the other was the control diet only (CG)	Significant alteration of the β-diversity of the WG compared with CG that accounted for 5 % of the dissimilarities between groups. Significant increase in relative abundance of *Ruminococcaceae* and *Bifidobacteria* in the WG compared with CG. Significant decrease in the relative abundance of *Blautia* and *Anaerostipes* in the WG compared with CG

Table 1. (*Continued*)

	Study	Design	Participants	Intervention/details	Impact on gut microbiota composition
Walnuts	Garcia-Mantrana *et al.*[51]	Pre-post parallel-arm intervention study	27 healthy adults	Participants were stratified into two groups depending on their urolithin metabolite (UM) profiles (UM-A *n* 14 or UM-B *n* 13). All participants consumed 33 g of walnuts per day for 3 consecutive days	Significant increase in the relative abundance of Bacteroidetes, and a significant decrease in Actinobacteria in both UM groups. Significant increase in the relative abundance of *Coprococcus* and *Collinsella* in both UM groups. Significant increase in the relative abundance of *Blautia* and *Bifidobacterium* in UM-B only. Significant decrease in the relative abundance of *Lachnospiraceae* in UM-A only
Wholegrains					
Wholegrains through diet	Roager *et al.*[121]	Randomised, controlled cross-over study	50 adults at risk for the metabolic syndrome (MetS)	Participants were randomised to begin in one of 2, 8-week dietary phases with a 6-week washout period between them. The whole grain diet (WG) included ≥ 75 g of whole grains/d and the refined grain (RF) was limited to ≤ 10 g of whole grains/d	No significant changes in diversity or the relative abundance of gut microbiota between dietary phases
Wholegrains through diet	Ampatzoglou *et al.*[122]	Randomised, controlled cross-over study	33 healthy adults	Participants were randomised to begin in one of 2, 6-week dietary phases: > 80 g/d of wholegrains through diet or < 16 g/d of wholegrains through diet. Participant diets were guided by the study dietitian and were separated by a 4-week washout period	No significant changes in diversity or the relative abundance of gut microbiota between dietary phases
Wholegrains through diet	Christensen *et al.*[123]	Pre-post parallel-arm intervention study	72 postmenopausal women with a BMI 27–37 kg/m^2	Participants were randomised to consume an energy-restricted diet of either a whole wheat diet (WW) (*n* 38) or refined wheat diet (RW) (*n* 34) for 12 weeks	No significant differences in microbiota composition between groups. WW group showed an increased relative abundance of *Bifidobacterium* compared with baseline
Wholegrain or wheat bran cereals	Costabile *et al.*[124]	Randomised, controlled, double-blind cross-over study	31 healthy adults with a BMI 20–30 kg/m^2	Participants were randomised to begin the study on either 48 g of whole grain (WG) or 48 g of wheat bran (WB) cereal for 3 weeks followed by the alternate cereal for 3 weeks after a 2-week washout period	Increased relative abundance of *bifidobacterial* and *lactobacilli* in WG phase compared with the WB phase
Wholegrain barley flakes and/or brown rice flakes	Martinez et al.[125]	Randomised cross-over study	28 healthy young adults	Participants followed 3, 4-week dietary phases (60 g daily whole grain barley flakes (WGB), 60 g brown rice flakes (BR) or 30 g of each (BR + WGB)) in random order, with a 2-week washout period between each intervention	All three dietary phases reported a significant increase in α-diversity and significant increase in the relative abundance of *Blautia*. Significant increase in the relative abundance of *Roseburia* in the WGB phase only
Fruits and vegetables					
Apples	Shinohara *et al.*[126]	Pre-post intervention study	8 healthy adult males	Participants consumed their habitual diet supplemented with 2 apples per day for 2 weeks	There was a significant increase in the relative abundance of *Bifidobacterium* and significant decrease in the relative abundance of lecithinase-positive *Clostridium*, and *Enterobacteriaceae*
Vegetables	Hiel *et al.*[127]	Pre-post intervention study	26 healthy adults	Participants followed a control diet enriched with inulin-type fructan-rich vegetables, ensuring that ≥ 9 g of fructans were consumed daily for 2 weeks	There was a significant increase in the relative abundance of *Bifidobacterium* and significant decrease in unclassified *Clostridiales*
Fruits and vegetables	Kopf *et al.*[128]	Randomised, controlled parallel-arm study	49 healthy adults with a BMI > 25 kg/m^2, with habitually low intakes of fruits and vegetables	Participants were randomised to incorporate fruits and vegetables (FV), whole grains (WG) or refined grains (control) into their usual diet, at 3 servings per day for 6 weeks	Significant increase in α-diversity in the FV group only

Table 1. (*Continued*)

	Study	Design	Participants	Intervention/details	Impact on gut microbiota composition
Fruits	Jaing *et al.* (129, 130)	Longitudinal	1879 healthy adults	Dietary data were collected using FFQ	Increased fruit intake was significantly associated with increased α-diversity
Raw fruits	Partula *et al.*[130]	Cross-sectional	862 healthy adults	Dietary data were collected using FFQ	Increased raw fruit intake was significantly associated with increased α-diversity and increased relative abundance of *Eubacterium eligens*
Red wine					
Red wine and de-alcoholised red wine	Moreno-Indias *et al.*[131]	Randomised, controlled, cross-over study	10 adult males with the metabolic syndrome (MetS) and 10 healthy adult males (control)	After a 2-week initial washout period, participants were randomised to begin the study consuming 272 ml/d of either red wine (RW) or de-alcoholised red wine (DRW) for 30 d, followed by the alternate intervention after a 15-d washout period	No significant differences in gut microbiota composition were reported between the two interventions. The MetS participants showed a significant increase in the relative abundance of *bifidobacteria*, L*actobacillus*, *Roseburia* and *Faecalibacterium prausnitzii* after RW and DRW consumption. Healthy participants showed a significant increase in the relative abundance of *Roseburia* and *F. prausnitzii* after RW and DRW consumption
Red wine, de-alcoholised red wine and gin	Quiepo-Ortuno *et al.*[132]	Randomised, controlled, cross-over study	10 healthy adult males	After an initial 15-d washout period, participants began the study consuming 272 ml/d of either red wine (RW) or de-alcoholised red wine (DRW) or 100 ml/d of gin (G) for 20 d, followed by the alternate interventions, in a randomised order	Significantly increased relative abundance of *Bacteroides, Bifidobacterium, Bacteroides uniformis, Eggerthella lenta, Blautia coccoides-Eubacterium rectale spp, Enterococcus* and *Prevotella* from red wine polyphenols (RW and DRW groups)
Red wine	Cuervo *et al.*[133]	Cross-sectional	38 healthy adults	FFQ was collected by a trained dietitian and correlations were investigated	Participants who regularly consumed red wine had significantly lower relative abundance of *Lactobacillus, Bifidobacterium, Blautia coccoides* and *Clostridium leptum*
Dairy					
Milk	Fernadez-Raudales *et al.*[134]	Randomised three-arm intervention study	64 male adults with a BMI > 25 kg/m^2	Participants were randomised into 1 of 3 intervention arms consisting of 500 ml/d of low glycinin soya milk (LGS (*n* 19)), conventional soya milk (S (*n* 23)) or bovine milk (M (*n* 22)) for 3 months	All three interventions showed decreased α-diversity after intervention. No significant changes in the relative abundance of species bovine milk intervention
Yogurt	Odamaki *et al.*[135]	Randomised, parallel-arm intervention study	32 healthy adults who were carriers of entero-toxic *Bacteroides fragilis* (ETBF)	After a 4-week run in, participants were randomised to consume either 200 ml UHT milk or 160 g of yogurt enriched with *Bifidobacteria longum* BB536 daily, for 8 weeks	Significant decrease in the relative abundance of ETBF in the yogurt group only
Yogurt	Odamaki *et al.*[136]	Randomised three-arm intervention study	31 healthy adults	All participants followed an animal-based diet for 5 d, followed by 14 d of a healthy balanced diet. Intervention was randomised into three groups. Group 1 consumed 200 g of yogurt enriched with *Bifidobacteria longum* both the animal-based phase and balanced diet phase (YAB), group 2 consumed the same yogurt during only the balanced diet phase (YB) and group 3 consumed no yogurt and was used as a control group (CTR)	The animal-based diet caused a significant increase in the relative abundance of *Bilophila, Dorea* and *Odoribacter* and a significant decrease in the relative abundance of *Bifidobacterium* in the YB and CTR groups. These changes were not seen in the YAB group
Mediterranean diet					
	Ghosh *et al.*[69]	Randomised controlled trial	612 non-frail and pre-frail elderly participants	Participants were randomised into intervention (NU-AGE diet) or control (habitual diet) for 1 year. The NU-Age diet is an individually tailored and culturally adapted version of a Mediterranean-style diet	Numerous bacterial taxa had a significant positive association with MD adherence and were reported as 'diet positive taxa'. This included *F. prausnitzii, Roseburia, members of the Eubacterium genus (E. rectale, E. eligens and E. xylanophilum), Bacteroides thetaiotaomicron* and *Anaerosipes hadrus*

Table 1. (*Continued*)

Study	Design	Participants	Intervention/details	Impact on gut microbiota composition
Meslier *et al.*[71]	Randomised controlled trial	62 healthy overweight or obese adults with a habitually low intake of fruits and vegetables	The intervention group (*n* 30) followed individually tailored MD that maintained the energy and macronutrients of the participant's habitual diet. The control group (*n* 32) maintained their habitual diet	Significantly increased relative abundance of *F. prausnitzii* and significantly decreased relative abundance of *Ruminococcus gnavus* and *Ruminococcus torques* in the MD group
Pagliali *et al.*[70]	Randomised cross-over intervention study	23 overweight omnivores with a low-moderate cardiovascular risk	Participants were randomly assigned to either a MD or vegetarian diet for 3 months before beginning the alternate diet for another 3 months	No significant differences in diversity or in phylum level relative abundance between the two diets. MD phase resulted in significantly increased relative abundance of *Enterohabdus* and *Lachnoclostridium* and a significant decrease in *Parabacteroides*
Haro *et al.*[68]	Randomised 2 × 2 factor intervention study	138 adults with MetS and 101 healthy adults	Participants from each group were randomised to follow either a MD or a low-fat high-carb diet for 2 years	MD induced increases in the relative abundance of *Parabacteroides distasonis, B. thetaiotaomicron, F. prausnitzii, Bifidobacterium adolescentis* and *B. logum* in the MetS group only. Weak but significant increases in *F. prausnitzii* and *B. adolescentis* for overall MD group
Luisi *et al.*[47]	Pre-post comparative intervention study	18 healthy adults with a BMI > 25 kg/m^2 and 18 healthy adult with a BMI 18–24·9 kg/m^2	Both BMI classification received a MD supplemented with 40 g of extra-virgin olive oil (EVOO) daily for 3 months. Participants with a BMI > 25 kg/m^2 diet were tailored to bed hypoenergetic	The relative abundance of lactic acid bacteria (LAB) was increased after the MD intervention. The increase in LAB was significantly higher in participants with a BMI > 25 kg/m^2
Zhu *et al.*[72]	Randomised cross-over study	10 healthy young adults	Participants were randomised to begin the study with a fast food (FF) intervention or MD intervention for 4 d before changing to the alternate intervention. Dietary phases were separated by a 4-d washout period	MD diet phase showed significantly increased relative abundance of *butyricicoccus* and *Lachnospiraceae_UCG-004,* and significantly decreased *Collinsella, Parabacteroides, Bilophila* and *Escherichia/Shigella* when compared with the FF diet phase
Galle *et al.*[65]	Cross-sectional	140 university students	Dietary data were captured using a 9-pt MD adherence score	High adherence to a MD was associated with increased relative abundance of *Lactobacillus, Lactococcus* and *Lachnospira*
De Filippis *et al.*[59]	Cross-sectional	153 healthy adults stratified by diet type. Vegan (*n* 51), Vegetarian (*n* 51), Omnivore (*n* 51)	Dietary data were collected using 7-d weighed food diary and 11-pt MD adherence score. Participants were stratified by diet type and MD score	No significant difference in microbiota between diet groups or MD score. Higher MD adherence was significantly correlated with higher levels of faecal SCFA
Garcia-Mantrana *et al.*[62]	Cross-sectional	27 healthy adults with a BMI > 30 kg/m^2	Dietary data collected using 140-item FFQ and 3-d weighed food diary	No significant difference in microbiota between diet groups or MD score. Higher MD adherence was significantly correlated with higher levels of faecal SCFA
Gutierrez-Diaz *et al.*[60]	Cross-sectional	31 healthy adults	MD adherence score was calculated from a FFQ	Higher MD adherence was significantly associated with *Bacteroidetes*, *Prevotellaceae* and *Prevotella* and was inversely associated with Firmicutes and *Ruminococcus.* Higher MD adherence was associated with increased levels of faecal butyrate and propionate
Mitsou *et al.*[61]	Cross-sectional	116 healthy adults	Dietary data were collected using a FFQ and 11-item MD adherence score	High adherence to a MD was significantly associated with decreased *Escherichia coli* counts, increased *Bifidobacterium/E.coli* ratio and increased faecal SCFA levels

MD, Mediterranean diet; MetS, metabolic syndrome.

lactic acid bacteria[64], which have been previously demonstrated to be beneficial to human health through their ability to enhance metabolism, protect against infections in the gastrointestinal tract and the ability to modulate both allergy and inflammatory responses[65]. This relationship was also demonstrated in a 3-month intervention study where participants followed a MedDiet supplemented with 40 g of EVOO per day showed an increase in the relative abundance of lactic acid bacteria. The magnitude of this effect demonstrated greater significance in overweight and obese participants[46]. Additional studies have highlighted the impact that participant obesity classification and metabolic status have on the gut microbiota's response to a MedDiet. A 2019 study in elderly obese women following a hypoenergetic MedDiet for 15 d showed a significant increase in α-diversity in participants with obesity class II (35–39·9 kg/m^2)[66], and in a subset of patients from the CORDIOPREV Study, where Haro and colleagues reported increases in the relative abundance of a number of species including *F. prausnitzii* and *Bifidobacterium longum* in the participants with the metabolic syndrome exclusively[67].

Recently, a large intervention study by Ghosh *et al.* was part of the NU-AGE 12-month randomised clinical trial and investigated the effects of a tailored MedDiet in relation to the gut microbiota and frailty in elderly participants (*n* 612) across five European countries[68]. While the authors reported no change in microbial diversity, there were changes in microbial composition that were positively associated with improved cognition and reduced frailty markers and negatively associated with inflammatory biomarkers C-reactive protein and IL-17. Many of the bacterial taxa associated with both adherence and inflammatory biomarkers were known SCFA producers. Similarly, the CARDIVEG study compared the gut microbiotas of participants after 3 months of either a Mediterranean or vegetarian diet and found significant changes in the relative abundance of several taxa in both groups. Interestingly, changes in the SCFA profile of the gut were observed exclusively in the MedDiet group[69]. These changes were also negatively associated with levels of pro-inflammatory biomarkers (IL-17 and IL-12)[69], again highlighting the relationship between the gut microbiota, SCFA production and inflammation.

Smaller, more short-term intervention studies have highlighted that beneficial changes in the gut microbiota can even be achieved over a short period of time. Messiler *et al.* found changes in microbiota composition, and increases in gene richness and faecal SCFA levels within the first 4 weeks on the MedDiet intervention[70], while Zhu and colleagues reported an increase in bacteria capable of producing SCFA in just 4 d of a MedDiet[71]. While these studies give evidence that alterations in the relative abundance of certain species of bacteria can be achieved in a limited time frame, these changes are likely transient in nature. Dietary studies with a cross-over design or those including follow-up analyses have shown that the microbiota reverts to pre-study composition a few weeks after the cessation of the dietary intervention[72–74]. A summary of the relevant studies can be found in Table 1.

Physical activity and the gut microbiota

Although there are numerous studies in murine models, research into the effects of PA on the gut microbiota of humans is limited to within the last decade. In the earliest study, Clarke *et al.* compared the gut microbiota of elite rugby players with that of healthy and high BMI control groups and the authors found increased microbiota diversity within the individual samples (α-diversity) of the rugby players, along with an increase in the relative abundance of several bacterial taxa, notably *Akkermansia muciniphila*[75], a mucin degrading bacteria from the *Verrucomicrobia* phylum involved in maintaining the integrity of the intestinal barrier, is negatively associated with impaired metabolic function and inflammation[76]. *A. muciniphila* abundance was also increased in the active participants of a 2017 study in premenopausal women, along with known butyrate producers *F. prausnitzii* and *Roseburia hominis*[77]. Other observational studies have also found correlations between levels of cardiovascular fitness and microbiota composition. Estaki *et al.* found increased α-diversity in participants with greater $VO_{2\ max}$[78], while Durk *et al.* reported significant correlation between $VO_{2\ max}$ and changes in the ratio of the two dominant phyla, Firmicutes and Bacteroidetes in a comparable population[79]. It should be noted that two of these studies reported significant dietary differences between groups, with the active participants having higher protein and fibre intakes than that of the controls. Consequently, the contribution of PA to the changes in the microbiota cannot be completely ascertained.

The small number of longitudinal studies on the topic so far have reported varying results. In a study conducted by Manukka and colleagues previously sedentary and overweight female participants (*n* 17) underwent 6 weeks of endurance exercise resulting in shifts in microbiota composition, including an increase in the relative abundance of the *Akkermansia* genus, but also noted that not all participants responded equally to the intervention[80]. A similarly designed study by Allen *et al.* that included lean and obese participants also reported changes in composition after the 6-week exercise period in the lean participants, with authors noting that changes were dependent on obesity status[81]. Contradictory evidence was found in another study looking at the effects of exercise and whey protein on the gut microbiota in overweight and obese participants (*n* 90), where no significant changes in composition were reported, potentially due to the varied obesity status of participants[82]. More recent and shorter longitudinal studies have also failed to provide definitive evidence on the subject. Motaini *et al.* investigated the effect that 2 weeks of sprint interval training or moderate-intensity continuous training had on the microbiota of twenty-six previously sedentary participants and reported a decreased Firmicutes: Bacteroidetes ratio by an increase of the relative abundance of that both training modalities of Bacteroidetes. Interestingly, the two methods of training had distinctive effects on the relative abundance of certain species, with sprint interval training and moderate-intensity continuous training resulting in an increase in *Lachnospira* and *F. prausnitzii,* respectively[83]. Conflicting results were reported in a 2020 study that found no significant changes in microbiota diversity or composition after 3 weeks of high intensity interval training in thirty-two male participants[84].

While there are several observational and longitudinal studies investigating the effects of PA on the microbiota, there is a paucity of evidence from randomised controlled trials outside of

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animal models. In one of the only randomised controlled trials conducted, Kern *et al.* implemented a 6-month trial comparing habitual PA and three exercise interventions: commute to work by bike, leisure time moderate exercise and leisure time vigorous exercise (n 88)[85]. While all three exercise groups had proportionate exercise-induced energy expenditure, increases in cardiorespiratory fitness and decreases in fat mass, only the vigorous exercise group showed a significant increase in α-diversity independent to fat mass and cardiorespiratory fitness. However, a potential limitation of this study as reported by the authors is that a change in dietary intake due to increased exercise cannot be ruled out as a contributing factor to microbiota composition changes.

Currently, there is limited research investigating the effects of PA on the elderly microbiota and studies so far have yielded varying results. In a 2017 cross-sectional study utilising data from the American Gut Project, Zhu *et al.* discovered a significant association between higher levels of self-reported PA and a decrease in microbiota α-diversity in overweight elderly (BMI > 25 kg/m) participants[86]. Interestingly, the authors also reported a positive association between α-diversity and increasing age, which contradicts numerous studies in the area[28,31,32]. In contrast, a smaller cross-sectional study (n 373) of elderly men found no association between α-diversity and PA levels; however, changes in microbial composition were reported[87] and Morita and colleagues compared 12 weeks of daily core muscle training or aerobic exercise on the gut microbiota of thirty-two elderly Japanese women, reporting a no change in α-diversity. However, significant increase in the relative abundance of Bacteroides was observed in the aerobic exercise group[88]. Studies detailing the impact of PA can be found in Table 2.

Gut microbiota in immune regulation and inflammation

The gut microbiota plays a crucial role in the development, maturation and regulation of the immune system. This intricate relationship begins at birth, where the immature immune system allows for the colonisation and expansion of the microbiota without inflammatory consequence, and immunological sensing of microbial molecules and metabolites allows for the development of food antigen tolerance and protective defences against pathogens concomitantly[89,90]. Perturbations in the development of the early relationship can have detrimental impacts on long-term health[91]. Given this interdependent relationship, age-related modifications of the gut microbiota may play a crucial role in the inflammation of ageing.

Studies directly investigating the effect of microbiota composition on inflammatory status have mostly been limited to animal models but have provided evidence that the aged microbiota can increase intestinal inflammation and permeability, and promote infiltration of microbes and microbial products into systemic circulation, which in turn can elevate pro-inflammatory biomarkers such as TNF-α and IL-6[92–94]. A human study analysing the gut microbiota of three age groups of Italian individuals reported major changes in the centenarian microbiota. Compared with younger cohorts, centenarians showed increases in the phyla Proteobacteria, which have been linked to increased inflammation and the onset of human disease and decreased relative abundance of *F. prausnitzii* and other SCFA producers. These changes were associated with increases in pro-inflammatory cytokines IL-6 and IL-8[31,95].

While the 2020 study by Ghosh and colleagues focused on the impact of a MedDiet on the gut microbiota, frailty and health outcomes, it also highlights the relationship between the microbial composition of elderly participants and their inflammatory status. The diet positive taxa identified were negatively associated with the levels of C-reactive protein and IL-17[68]. These results strengthen the theory that gut microbiota composition has an impact on inflammatory outcomes and demonstrate the ability of a MedDiet to induce favourable changes in the ageing gut microbiota.

Microbiota-mediated impacts on inflammation can occur in multiple pathways through various systems, molecules, receptors and cells. The high dietary fibre content of the MedDiet gives rise to an increase in SCFA, the most investigated microbial metabolites, which are capable of acting both locally and systemically. In the gut, they play a critical role in maintaining the integrity of the intestinal barrier as they provide an energy source for colonocytes and have a regulatory role in the expression of tight junction proteins[96]. As seen in murine models, if the intestinal barrier is compromised, potentially harmful microbes and microbial products can infiltrate systemic circulation, inducing the inflammatory response and contributing to immune dysregulation[93,94]. Further, SCFA also promote the conversion of naïve T cells into forkhead box P3 (Foxp3$^+$) and IL-10 secreting regulatory T cells (Tregs) and interact with intestinal and peripheral innate immune cells via inhibitory effects on histone deacetylase and NF-κB, leading to down-regulation of gene expression for pro-inflammatory cytokines like TNF-α, IL-6 and IL-1[62,97]. Recent work has begun to investigate the microbial metabolites of additional substrates including dietary polyphenols and amino acids. The majority of dietary polyphenols, known for their antioxidant and anti-inflammatory potential, reach the large intestine intact where they undergo transformation into bioavailable compounds by the gut microbiota[98,99]. These compounds, including protocatechuic acid and urolithins, are able to enter circulation and influence the inflammatory response through mitogen-activated protein kinase and NF-κB pathways[100,101]. Additionally, the gut microbiota plays a central role in the metabolism of the amino acid tryptophan into various catabolites including kynurenine, indolic compounds, tryptamine and serotonin[102]. The majority of dietary tryptophan is fed into the kynurenine pathway, leading to the creation of various end products that are involved in a host of physiological responses including neurotransmission, and immune system and inflammatory regulation[102,103]. One mechanism by which this is achieved is through the activation of the aryl hydrocarbon receptors that are highly expressed in immune cells. The activation of aryl hydrocarbon receptors plays an essential role in T cell differentiation into immunomodulatory Tregs, leading to the down-regulation of inflammation[98,104]. The relationship between the kynurenine pathway, gut microbiota and the immune system is complex, with inflammatory mediator and microbiota signalling impacting the production of kynurenine pathway end

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Table 2. Summary studies assessing the impact of physical activity status or an exercise intervention on the human gut microbiota

Study	Design	Participants	Exercise training	Dietary differences or controls	Impact on gut microbiome composition
Kern *et al.*[86]	Randomised controlled trial	Adults with overweight or obesity. CON – Habitual group (*n* 14). BIKE – Commute by bike (*n* 19). MOD – Moderate intensity leisure time activity (*n* 31). VIG –Vigorous activity intensity leisure time activity (*n* 24)	5 training days per week equalling to a weekly energy expenditure of 6695 kj (1600 kcal) for female and 8786 kj (2100 kcal) for males	Self-reported dietary intake remained the same in all exercise groups with the exception of increased fibre consumption at 3 months, and decreased fat consumption at 6 months in the MOD group. Non-statistical	Increased α-diversity in all exercise groups when compared with the control group
Clarke *et al.*[76]	Cross-sectional	Elite rugby players (*n* 40). Low BMI (lean sedentary) controls (*n* 23). High BMI controls (*n* 23)	N/A	The diet of rugby players was significantly higher in total energy content and protein than in both controls. Increased protein consumption accounted for many of the differences in microbiota composition	The α-diversity of the gut microbiome in athletes was greater when compared with low BMI controls. Increased relative abundance of *Akkermansia* in athletes and low BMI controls
Bressa *et al.*[78]	Cross-sectional	Women 18–40 years with a BMI 20–25 kg/m^2. Active (> 3 h physical activity per week *n* 19). Sedentary (< 30 min 3 times per week *n* 21)	N/A	The active group reported higher intake of fruits and vegetables than the sedentary group. The sedentary group reported higher intake of processed meats than the active group	Increased relative abundance of *R. hominis, A. muciniphila* and *F. Prausnitzii*, and decreased relative abundance of *Odoribacteraceae* and *Barnesiellaceae*
Estaki *et al.*[79]	Cross-sectional	Healthy young adults with varying levels of cardiorespiratory fitness (*n* 39)	N/A	No significant differences in dietary intake were reported. Protein intake was significantly associated with microbiota composition	Participants with higher levels of physical fitness (measured by VO_2peak) had increased relative abundance of butyrate-producing taxa *Lachnospiraceae, Roseburia* and *Clostridiales.* Higher physical fitness accounted for 20 % of the variation in species richness. Increased faecal butyrate concentration
Durk *et al.*[80]	Cross-sectional	Healthy young adults with varying levels of cardiorespiratory fitness (males *n* 20, females *n* 17)	N/A	No significant associations were reported between dietary intake and gut microbiota composition	VO_{2max} was significantly correlated with a higher ratio of Firmicutes to Bacteroidetes. VO_{2max} accounted for 22 % of the variation in gut microbiota composition
Langsetmo *et al.*[88]	Cross-sectional	Community-dwelling older men (*n* 373) stratified into quartiles by step count. Q1 steps (*n*), Q2 steps (*n*), Q3 steps (*n*), Q4 steps (*n*)	N/A	No significant associations between dietary intake and gut microbiota composition	Higher step counts were correlated with a reduced relative abundance of *Coprobacillus*, *Adlercreutzia* and *Erysipelotrichaceae,* and increased relative abundance of *Cetobacterium*
Zhu *et al.*[87]	Cross-sectional	1589 healthy adults, 897 elderly adults stratified by exercise frequency, Daily (*n* 194), Regular (*n* 360), Occasional (*n* 209), Rare (*n* 102), Never (*n* 32)	N/A	No dietary data were collected	Microbiota composition of elderly adults who participated in daily exercise was most similar to that of healthy younger adults. Increased relative abundance of numerous microbial metabolism pathways in the daily/regular exercise groups when compared with rarely/never exercise groups. After stratification for BMI, obese participants who participated in daily/regular exercise did not show the BMI associated

Table 2. (*Continued*)

Study	Design	Participants	Exercise training	Dietary differences or controls	Impact on gut microbiome composition
					changes seen in those who rarely/ never engaged in exercise
Allen *et al.*	Pre-post intervention study	32 previously sedentary adults (lean *n* 18, obese *n* 14)	6-week progressive endurance training intervention followed by a 6-week sedentary washout period	Habitual dietary intake was maintained throughout the study and was confirmed by a 7-d food diary. A control diet that matched habitual intake was prescribed for 3 d prior to faecal sample collection.	Changes in various taxa were dependent on BMI status. *Bacteroides* decreased in lean participants but increased in obese participants. *Faecalibacterium* increased in lean participants but decreased in obese participants
Munukka *et al.*[81]	Pre-post intervention study	Previously sedentary overweight women (*n* 19)	6-week low-moderate intensity cycling programme	Habitual diet was confirmed to be maintained by 3-d food diary	Increased relative abundance of *Akkermansia* and decreased relative abundance of *Proteobacteria.* Decreased microbial genes related to the metabolism of amino acids and fructose
Cronin *et al.*[83]	Pre-post comparative intervention study	Healthy young adults with a BMI 22–35 kg/m^2 randomised into three groups. Whey protein only (*n* 30). Exercise and whey protein (*n* 30). Exercise only (*n* 30)	8-week progressive programme of moderate aerobic exercise and resistance training 3 times per week	Self-reported maintenance of habitual diet	No significant changes in relative abundance
Motaini *et al.*[84]	Pre-post comparative intervention study	26 previously sedentary, insulin resistant participants randomised into different exercise methods	2 weeks of either sprint interval training (SIT) or moderate-intensity continuous training (MICT) 3 times per week	No dietary control	Increased relative abundance of Bacteroidetes phylum, and decreased Firmicutes:Bacteroidetes ratio. Decreased relative abundance on *Clostridium* and *Blautia.* Increased relative abundance of *Lachnospira* in the SIT group
Rettedal *et al.*[85]	Pre-post intervention study	32 previously sedentary adult men with a BMI 20–25 kg/m^2 (*n* 14) and 28–35 kg/m^2 (*n* 15)	3 weeks of high intensity interval training (cycling) 3 times per week	Maintenance of habitual diet was maintained according to FFQ	No significant associations found between cardiorespiratory fitness and microbiota composition
Morita *et al.*[89]	Non-randomised comparative	32 previously sedentary elderly females allocated to either aerobic exercise or trunk muscle strength training groups	12 weeks of either 1 h/d of trunk muscle strengthening exercises or 1 h/d of brisk walking	No significant difference between the dietary intake of both groups at baseline and after intervention	Increased relative abundance of *Bacteroides* in both groups. Increased *Clostridium cluster IX* in trunk muscle exercise group. Decreased *Clostridium subcluster XIVa* in aerobic exercise group. Time spent during brisk walking significantly correlated with increased relative abundance of *Bacteroides*

products[105,106]. This tri-directional communication warrants further research to fully elucidate clinical implications.

In addition to the direct interaction with immune cells, the gut microbiota also engages in bidirectional communication with the brain via the gut–brain axis that is comprised of neural, endocrine, immune and metabolic pathways. Initial research focused on the role of the gut–brain axis in hunger and satiety signalling but has now expanded to exploring its role in conditions including irritable bowel syndrome, depression and anxiety, autism spectrum disorder and neurodegenerative diseases[107–109]. One way in which the gut–brain axis can influence inflammation is through the cholinergic anti-inflammatory pathway[110]. The vagus nerve, which is comprised of both afferent and efferent nerve fibres, has fibres that innervate the intestinal wall. While these fibres do not extend into the intestinal lumen, microbial compounds and metabolites can diffuse across the gut barrier where they can activate the vagus nerve, with the resulting signal is processed by the central nervous system[111]. The proceeding efferent signalling of the vagus nerve results in decreased cytokine secretion by immune cells, including macrophages, dendritic cells and T-cells, through the binding of the neurotransmitter acetylcholine to their nicotinic receptors, heavily influencing intestinal homoeostasis and immune responses[111,112].

Knowledge gaps and future directions

The current breath of evidence suggests that both a MedDiet and PA may modulate the gut microbiota composition in a way that is beneficial to host health. However, the majority of studies have been cross-sectional or longitudinal in design and have had wide variation in duration, participant characteristics and outcome measurements, making conclusions regarding causality challenging. There is a definitive need for further well-designed RTC to elucidate a sufficient understanding of the topic. There is also a current gap in the literature investigating the combined effect of these interventions, and to identify any synergistic effects this combination may have on microbiota composition.

Changes in the composition and function of the ageing microbiota have been well demonstrated in the literature so far, and further investigation into the association of these perturbations and the chronic inflammation seen in ageing is warranted. So far, only the NU-AGE project has evaluated the effect of the MedDiet, microbiota and healthy ageing outcomes and additional studies are required to build a body of knowledge capable of influencing healthy ageing strategies.

Conclusion

There is an abundance of literature demonstrating the health benefits of a MedDiet and lifestyle through various stages of life. Comprised of high intakes of fibre, polyphenols and beneficial fatty acids, it is plausible that some of these benefits can be attributed to gut microbiota modulation. As research continues, the role of the gut microbiota in human health is being further elucidated and the intricate relationship between the gut microbiota and the immune system has been brought to the forefront. Although the aetiology of age-related diseases is multi-factorial in nature, involving a multitude of molecular mechanisms, we propose that the beneficial modification of the ageing gut microbiota by utilising a combination of a MedDiet and PA may be a powerful strategy in attenuating age-related inflammation and improving health during a person's later years of life.

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