The anti-inflammatory effects of a Mediterranean diet: a review

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Purpose of review
Chronic noncommunicable diseases remain the leading cause of morbidity and mortality worldwide and the majority are preventable with a healthy diet and lifestyle, but controversy remains as to the best approach. Greater adherence to a traditional Mediterranean diet has consistently been associated with lower morbidity and mortality from cardiovascular disease, diabetes and many cancers, and lower all-cause mortality. Despite the well known benefits on chronic disease risk there remains some scepticism as to the effects of this dietary pattern across populations outside the Mediterranean and the mechanisms of action of this traditional plant-based dietary pattern.
This narrative review aims to summarize the latest evidence on the health protective effects of a traditional Mediterranean diet on chronic noncommunicable diseases, specifically focussing on the anti-inflammatory effects of this highly published dietary pattern.

Recent findings
Recent high-quality evidence now supports a Mediterranean diet in secondary prevention of cardiovascular disease with impacts on atherosclerosis progression, likely through reduction of systemic inflammation and irrespective of changes in cholesterol or weight. The Mediterranean diet has a low Dietary Inflammatory Index illustrating its anti-inflammatory potential. This dietary pattern beneficially modulates the gut microbiota and immune system, including emerging evidence for efficacy against severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019). Emerging evidence shows clinicians are not routinely recommending a Mediterranean diet despite well known evidence due to barriers such as lack of training, patient materials and concerns about potential patient adherence.

Summary
The physiological mechanisms of action of this healthy diet pattern are becoming better understood to be multisystem and involving the gut. Larger controlled trials investigating mechanistic effects in broader non-Mediterranean populations are warranted. Although reflected in therapeutic guidelines for chronic disease management worldwide there are individual, clinical practice and health system barriers to its implementation that need a multisectoral approach to address.

Keywords
antioxidants, coronavirus disease 2019, gut microbiome, inflammation, Mediterranean diet, polyphenols

INTRODUCTION

Chronic noncommunicable diseases account for the majority of morbidity and mortality worldwide, yet studies show that ~40% of all burden of disease is preventable with modifiable lifestyle risk factors [1,2]. Human life expectancy has continued to increase over the past century due to extensive public health measures, however, as we

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Curr Opin Clin Nutr Metab Care 2022, 25:415–422

DOI:10.1097/MCO.0000000000000872

KEY POINTS

- Many healthy dietary patterns across the world have been associated with health and longevity, however, the largest body of published evidence is attributed to the traditional Mediterranean dietary pattern.
- A growing body of observational and intervention trial evidence supports that Mediterranean diet exerts anti-inflammatory effects.
- The Mediterranean diet beneficially modulates the gut microbiota and immune system, including emerging evidence for efficacy against severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019).
- The Mediterranean diet has a low Dietary Inflammatory Index illustrating its anti-inflammatory potential.
- Emerging evidence shows clinicians are not routinely recommending a Mediterranean diet despite well known evidence due to barriers such as lack of training, patient materials and concerns about potential patient adherence.

live longer chronic diseases such as cardiovascular disease (CVD), obesity, diabetes, neurodegenerative diseases and cancers have increased resulting from longer term exposure to poor lifestyles such as inactivity, unhealthy diets and smoking. Furthermore, ageing is associated with low-grade chronic inflammation called *inflammaging*, which has been defined as the gradual inability to deal with endogenous and exogenous stressors and an increase in pro-inflammatory markers which predispose to chronic diseases and morbidity and mortality [3]. Consistently, research across the globe has shown that a majority of mortality from CVD can be prevented with modifiable lifestyle risk factors such as healthy dietary patterns, rich in plant foods like the Mediterranean diet.

This narrative review aims to summarize the current evidence on the protective effects of a traditional Mediterranean diet on chronic disease risk and in the promotion of longevity and explore the physiological mechanisms with a specific focus on the anti-inflammatory effects of this traditional dietary pattern.

What is a traditional Mediterranean diet and what are the known health benefits?

Over the past few decades the literature on the beneficial effects of a Mediterranean diet has grown exponentially. However, many systematic reviews and meta-analyses of clinical intervention trials have identified that there are many definitions of a Mediterranean diet and one could argue as many as there are countries surrounding the Mediterranean. Although there are now well established and validated scoring systems to assess adherence to a Mediterranean diet which have been used extensively in observational studies, it is important to have a clear definition when designing clinical intervention trials to ensure all the elements of this protective dietary pattern are included. Our work has focussed on the archetypal 'Cretan' Greek Mediterranean diet as originally described by Ancel Keys in the Seven Countries study, illustrated in the following definition.

The traditional Mediterranean diet is a plant-based diet which is abundant in seasonal vegetables and fruit, legumes, nuts, extra virgin olive oil used as the main source of added fat, wholegrain cereals often consumed as sourdough bread, moderate portions of fish 2–3 times weekly, fermented dairy consumed mainly as yoghurt and feta cheese most days, red meat and processed meats consumed sparingly with a preference for white meats (chicken) and game meats, free range eggs three to four times per week, fresh and dried herbs and spices, and fresh lemon juice used to flavour salads and cooked meals, water as the main beverage and wine in moderation and always with meals [4,5▪]. The health benefits of this dietary pattern extend to important lifestyle and cultural factors such as growing and harvesting foods, processing such as fermenting and cooking, and sharing foods while eating together. These important lifestyle factors led UNESCO in 2010 to include the Mediterranean diet on the list of the intangible cultural heritage of humanity [6].

The health benefits of the Mediterranean diet have been known for over 50 years beginning with the findings of the landmark Seven Countries study demonstrating that the lower cardiovascular mortality of Greek Mediterranean people was associated with their nutritional intake [7]. Research has consistently found that greater adherence to a Mediterranean diet is associated with a lower risk of heart disease and stroke, type 2 diabetes, certain cancers, neurodegenerative diseases such as Alzheimer's and other dementias, and reduced all-cause mortality [8]. An umbrella review of observational studies and randomized controlled trials involving more than 12.8 million people around the world investigated the association between Mediterranean diet adherence and 37 different health outcomes [9]. These studies found that for every point increase in the score of adherence to a Mediterranean diet (0 being no adherence and 9 being total adherence) there was a 10% reduction in risk of death from heart disease, cancer (breast and prostate cancers in particular),

Alzheimer's disease and other forms of dementia, neurodegenerative diseases such as Parkinson's disease, diabetes, stroke and death from any cause.

A recent umbrella review of 495 unique meta-analyses of randomized clinical trials examined the effects of a wide range of popular diets including low-carbohydrate, high protein, palaeolithic, low glycaemic index, intermittent energy restriction, Nordic, vegetarian, Dietary Approaches to Stop Hypertension (DASH), portfolio and Mediterranean diets on anthropometric parameters and cardiometabolic risk factors. This extensive review found that the Mediterranean diet had the strongest and most consistent evidence of beneficial effects on these chronic disease parameters [10▪▪]. Many healthy dietary patterns across the world have been associated with health and longevity, however, the largest body of published evidence is attributed to the traditional Mediterranean dietary pattern. Dietary guidelines and chronic disease specific guidelines are now identifying the Mediterranean diet as an optimal dietary approach for health maintenance and disease prevention. The Mediterranean diet was designated in the 2015–2020 Dietary Guidelines for Americans among the healthiest dietary patterns recommended [11]. Guidelines from the American Heart Association, Australian National Heart Foundation and European Society of Cardiology all consistently highlight the Mediterranean diet as a healthy dietary pattern in promotion of heart and metabolic health [12–14]. Despite the body of evidence in support of a Mediterranean dietary pattern, however, population adherence to this pattern is not strong, even in Mediterranean countries [15]. Furthermore, recent evidence shows that specialist clinicians and dietitians are not routinely recommending this dietary pattern for management of common chronic diseases such as diabetes and cardiovascular disease [16▪,17].

The mechanisms by which a traditional Mediterranean diet exerts protective effects across multiple chronic disease pathways are multifactorial. Originally this traditional dietary pattern was thought to be protective due to the cardioprotective fatty acid profile, namely rich in monounsaturated fatty acids from extra virgin olive oil, the primary source of dietary fat, and the long chain omega-3 fatty acids eicosapetanenoic acid and docosohexaenoic acid from fish and seafoods and their precursor alpha-linolenic acid from nuts and wild edible plants. More recently, the proposed protective mechanisms are thought to be due to the reduction of oxidative stress and chronic inflammation attributable to the bioactive phytonutrients with antioxidant and anti-inflammatory potential sourced from this plant-based biodiverse dietary pattern.

Current evidence on Mediterranean diet and inflammation

A growing body of observational and intervention trial evidence supports that a Mediterranean diet exerts anti-inflammatory effects. A recent systematic review of observational studies reported on associations between dietary patterns and inflammatory biomarkers in the general adult population [18]. Higher adherence to the Mediterranean diet (assessed in 14 studies) was significantly associated with lower levels of inflammation, including a reduction in pro-inflammatory biomarkers able to be detected in the systemic circulation such as C-reactive protein (CRP), interleukin-6 (IL-6) and fibrinogen. Another recent systematic review reported on associations between dietary patterns and biomarkers of oxidative stress and inflammation, however they had an expanded population criteria with 5 of 16 observational studies involving participants with an underlying cardiometabolic condition [19]. Mediterranean diet adherence was associated with improved concentrations of oxidative stress markers (e.g., F2-isoprostane and total antioxidant capacity) and pro-inflammatory biomarkers. This review additionally reported outcomes from intervention studies and found that only Mediterranean and DASH dietary patterns had a significant effect on inflammatory biomarkers.

Meta-analyses specifically on randomized control trials (RCTs) of dietary patterns and their effects on biomarkers of inflammation was published in 2022 [20▪▪]. The authors concluded that the Mediterranean diet appeared as the dietary pattern with the most prominent reductions of inflammatory biomarkers, which included significant improvements in IL-6 (pooled mean difference −1.07 pg/ml) and CRP (pooled mean difference −1.00 mg/l). The 16 Mediterranean diet RCTs were 4 weeks to 5 years duration and had varied populations including healthy older adults, as well as adults with prostate cancer, CVD risk factors, osteoarthritis, coronary heart disease or type 2 diabetes. No substantial effects were observed for other dietary pattern interventions, including DASH, vegetarian or vegan diets.

It is well established that atherosclerosis is an inflammatory process and biomarkers such as CRP and IL-6 are associated with increased risk of acute coronary events [21]. This suggests that the effect of a Mediterranean diet on these pro-inflammatory biomarkers is likely associated with reducing risk of CVD. Recently published data from a landmark secondary prevention single-blinded randomized controlled trial, the CORDIOPREV study, supports this. In 1002 people with existing coronary heart disease, it was demonstrated that adjunct to usual treatment, Mediterranean diet intervention significantly reduced risk of composite major cardiovascular

events compared with low-fat diet after 7 years (hazard ratio [HR] 0.734 (0.55–0.97) in the total cohort and HR 0.67 (0.49–0.92) in men) [22▪▪]. Aligned to these clinical outcomes, the Mediterranean diet significantly decreased markers of atherosclerosis progression compared to the low-fat diet, including reduction in intima-media thickness of both common carotid arteries and carotid plaque height [23]. Importantly, in this secondary prevention cohort who were receiving standard medical treatment, there was no effect of dietary intervention on cholesterol, blood glucose levels or weight [22▪▪], which postulates that the Mediterranean diet influenced atherosclerosis through other mechanisms such as reducing circulating inflammation [24].

Are the anti-inflammatory effects of a Mediterranean diet mediated via the gut?

The Mediterranean diet is high in polyphenols, which are bioactive compounds found only in food and drinks sourced from plants, and which have antioxidant and anti-inflammatory properties [25,26▪]. Within the Mediterranean diet, polyphenols come from its rich content of fruit, vegetables (particularly herbs and spices), wholegrains, nuts, seeds and legumes. Furthermore, extra virgin olive oil and red wine (which are not typically included in other types of diets) contain the polyphenols hydroxytyrosol, tyrosol, oleocanthal and resveratrol that have postulated anti-inflammatory properties. The Mediterranean diet also includes very low amounts of processed foods, high sugar drinks and red meat which are pro-inflammatory [27]. Thus, the anti-inflammatory effect of following a Mediterranean diet is related to the dietary pattern as a whole, not just its individual components.

Over the past decade, researchers have made steady gains in understanding the interactions between diet, human body (host) and gastrointestinal tract microbiota and health status. Importantly, many pathological conditions linked to low-grade chronic inflammation are characterized by an imbalance (dysbiosis) of the gut bacterial composition. The dysbiotic phenotype is often associated with the host having a so-called 'leaky gut' whereby both bacteria and toxins can breach the endothelial cell lining of the intestine and enter the systemic circulation causing metabolic endotoxemia and widespread inflammation.

The Mediterranean diet beneficially modulates the gut microbiota and the immune system (Fig. 1). By comparing the bacterial DNA from fecal samples, studies in populations such as obese individuals have demonstrated that a sustained Mediterranean diet dynamically modulates the gut microbiome composition to the benefit of human health, in particular improving the diversity of bacterial species present and their metabolic activities [28▪]. The evidence suggests that polyphenols themselves influence the ratio of beneficial versus harmful bacteria taxa [26▪]. Beneficial bacteria are nourished by polyphenols with antioxidant potential and dietary fibre, which serves as a prebiotic for the microbial growth of bacteria living in the host. Specifically, soluble dietary fibres from legumes, fruits and vegetables and grains found abundantly in a Mediterranean dietary pattern, have been shown to benefit intestinal microbiota. Composed of carbohydrate polymers, these fibres reach the large intestine undigested (as they cannot be degraded by human enzymes), whereupon they are metabolized by gut microorganisms into oligosaccharides and monosaccharides. These simpler sugars serve as growth substrates for beneficial microbes that protect the integrity of the intestinal barrier [29▪▪,30]. The microbiota further metabolize (ferment) these sugars into short-chain fatty acids (SCFAs) which are absorbed into the blood stream leading to beneficial metabolic effects [29▪▪].

The Mediterranean diet is high in both prebiotic (e.g. legumes and wholegrains) and probiotic (e.g. yoghurt and feta cheese) foods. A higher adherence to the Mediterranean diet is associated with greater production of SCFAs by beneficial bacteria in the gut and these fatty acids are absorbed into the blood stream and are associated with reduced risk of chronic diseases [28▪]. A higher adherence to the Mediterranean diet is also associated with lower levels of trimethylamine N-oxide (TMAO) a molecule generated by gut microbial metabolism that has pro-inflammatory effects and is associated with atherosclerosis [26▪]. Furthermore, gut bacterial taxa enriched by adherence to the Mediterranean diet have been negatively associated with inflammatory markers including CRP and IL-17 [30]. Modulating endocannabinoid tone may represent a new avenue whereby the Mediterranean diet ameliorates systemic inflammation. Increased activity of endocannaboids plays a role in regulation of energy intake and storage. In a recent intervention RCT in overweight and obese individuals, circulating levels of endocannabinoid AEA (Arachidonoylethanolamide) decreased with Mediterranean diet, associated with increased *Akkermansa muciniphila* abundance in the gut (a bacterium known to contribute to gut health) [31].

Emerging evidence for anti-inflammatory effects of Mediterranean diet on other health conditions

Unlike other popular dietary interventions which target specific health conditions, the traditional

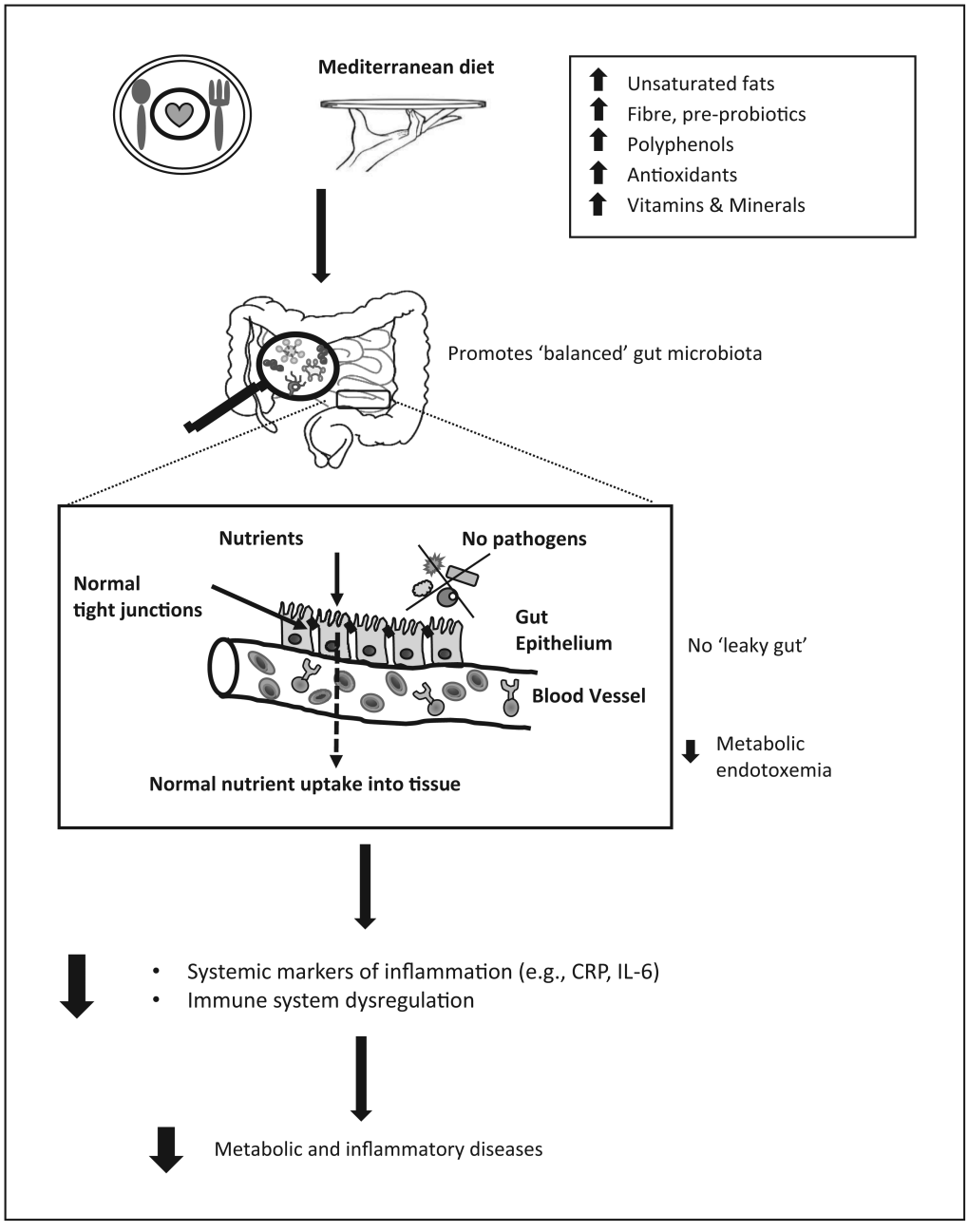

FIGURE 1. The plant-based Mediterranean diet beneficially modulates the gut microbiota and immune system. This dietary pattern is high in bioactive components and healthy nutrients which promote a balanced bacterial community in the gastrointestinal tract and limits opportunistic bacteria. Gut microbiome diversity supports healthy gut epithelial function, normal nutrient uptake into tissue and counteracts metabolic endotoxemia (lipopolysaccharide in the bloodstream) and other bacterial metabolites which stimulate inflammatory responses and contribute to metabolic and inflammatory diseases. CRP, C-reactive protein; IL-6, interleukin-6.

Mediterranean dietary pattern has consistently been shown to exert health benefits across multiple chronic diseases. In our studies, we have evaluated the health impacts of this dietary pattern across multiple chronic diseases including type 2 diabetes, metabolic syndrome, nonalcoholic fatty liver disease, coronary heart disease, dementia, and asthma effectively illustrating that there is a multisystemic effect of this dietary approach.

Current synthesis of the literature from observational and intervention studies also supports that there is emerging evidence for a positive effect of a Mediterranean diet in patients with immune-mediated inflammatory conditions such as inflammatory

bowel diseases, rheumatoid arthritis and psoriasis [32,33]. Given the mechanisms of action of a Mediterranean diet pattern is likely via its anti-inflammatory potential, clinical trials investigating its impact on chronic debilitating and highly prevalent conditions such as rheumatoid arthritis are underway [34].

The coronavirus disease (coronavirus disease [COVID-19]; caused by a severe acute respiratory syndrome coronavirus 2 [SARS-Cov-2]) pandemic has high rates of infection, morbidity and mortality and has caused severe global impacts to health and the economy. This highly infective virus is strongly associated with inflammation and thrombosis with multiorgan effects, predominantly in the lung. Emerging research shows a strong association between COVID-19 severity and nutritional status [35], with a recent longitudinal study of over 5000 (non health professional) participants from the SUN Cohort Longitudinal Study in Spain showing that higher adherence to a Mediterranean diet was associated with a significant 35% reduction in risk for COVID-19 infection [36]. COVID-19 pathophysiology is associated with platelet activating factor (PAF) which is a potent mediator of inflammation and thrombosis. It is possible that an anti-inflammatory diet like the Mediterranean diet may be protective via modulation of PAF. Dietary inhibitors of PAF have been identified in natural products and diets with anti-inflammatory nutrients such as a Mediterranean diet [37].

Assessing the anti-inflammatory potential of the Mediterranean diet

Evaluating diet quality through macronutrient and micronutrient analysis, or qualitatively through food group analysis or standardized diet scores can be limited and does not necessarily identify the anti-inflammatory elements of a dietary pattern.

The Dietary Inflammatory Index (DII) provides a noninvasive and inexpensive method of estimating the likely influence of dietary intake on inflammation in the body and scores a person's diet on a continuum from maximally anti-inflammatory (−9) to proinflammatory (+8). Since being published in 2014, the DII has astonishingly already been reported in around 500 papers. This includes recent evidence syntheses demonstrating a significant association between high DII score and risk of CVD incidence and mortality [39], all-cause mortality and overall cancer risk [40▪]. Importantly, however there is a significant lack of intervention studies designed to improve DII and assess its effect on cardiometabolic disease risk [38]. Much of the literature also lacks application of how DII (which is largely based on nutrients) could be translated to dietary recommendations. Importantly, our prospective application of the DII to RCT data in people with coronary heart disease demonstrated that 6-month Mediterranean diet intervention significantly improved DII score (by mean -1.34 points, to be more anti-inflammatory) compared to a low-fat diet which had no influence on DII score [41]. We also found that change in DII score was associated with improved IL-6 levels [42]. Adherence to key Mediterranean dietary components which were associated with improved DII were intake of extra virgin olive oil, vegetables, legumes, nuts, sofrito based dishes, and limited red meat.

Practical applications of a Mediterranean diet in reducing inflammation

Whilst studies support that a Mediterranean diet exerts anti-inflammatory effects and can reduce risk of a variety of health conditions, research evidence alone is not sufficient to translate these findings into clinical practice [5▪]. Recent studies in non-Mediterranean settings have demonstrated that despite a Mediterranean diet being consistently recommended across clinical guidelines for cardiometabolic conditions, it may not be routinely recommended to patients by clinicians [16▪,17]. Dietitians reported that food principles aligned to a Mediterranean diet which they less frequently recommended to patients included liberal use of extra virgin olive oil, substantial reduction in red meat and regular intake of plant-based protein sources, regular intake of tomatoes, and regular use of onion, garlic and other herbs and spices. These principles make important contributions to the anti-inflammatory and antioxidant properties of the dietary pattern. Furthermore, the focus of clinicians' understanding of the role of diet in disease appears to remain limited to traditional risk factors such as cholesterol and blood glucose, and not potential broader inflammatory or oxidative stress impacts. Clinicians from across disciplines highlighted important practice barriers, including understanding of evidence, nutrition skills training, access to practical patient education materials, time and resources constraints, and lack of belief in patient capabilities to improve dietary adherence. These barriers need to be addressed in order that the anti-inflammatory effects of a Mediterranean diet may be realized for patients outside of controlled trials.

CONCLUSION

Achieving strong and sustained adherence to a healthy diet and lifestyle pattern is the panacea to chronic disease prevention and healthy longevity. The health benefits of a Mediterranean dietary pattern are now well established and the physiological mechanisms of action of this healthy diet pattern are

becoming better understood to be multisystem and involving inflammation and the gut. In particular, phytochemicals and dietary fibre in the food groups which feature as staples in the Mediterranean diet (vegetables, fruits, wholegrains, legumes, nuts and olive oil) favourably influence host health via anti-inflammatory and antioxidant properties as well as gut microbiome compositional and functional changes. There is now a strong rationale to integrate the human gut microbiome in contemporary Mediterranean diet research to build evidence of mechanistic and causal contributions of the microbiome to the physiological effects of the diet. Worldwide dietary guidelines have identified the Mediterranean diet as one of the healthiest in prevention of multiple chronic diseases however, as we have noted, health practitioners are not routinely prescribing this diet due to multiple factors including lack of evidence on non-Mediterranean populations, lack of training in health professions on how to implement and practical resources within the health setting for its effective implementation. There is a missed opportunity in clinical practice to apply this highly palatable and sustainable dietary intervention with multiple health benefits to manage patients with co-morbidities. Achieving widespread application of the principles of a Mediterranean diet requires a multisectoral approach and further robust evidence of its effectiveness in a broader multicultural and non-Mediterranean setting.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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