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REVIEW



Adherence to the Mediterranean diet and healthy ageing: Current evidence, biological pathways, and future directions

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ABSTRACT

With an ever-ageing population in developed countries, healthy ageing is an emerging public health priority for securing citizens' quality of life and minimizing healthcare associated costs. While adherence to the Mediterranean diet is associated with numerous health benefits and deterrence of age-related disorders, a comprehensive review of the current evidence to guide further public health interventions is lacking. This study systematically assessed, according to PRISMA guidelines, current evidence arising from observational studies regarding the potential impact of adherence to the Mediterranean diet on healthy ageing among elder adults. Of 509 initially retrieved unique items, 9 studies (including 2 cross-sectional and 7 prospective cohort studies) were reviewed. The reviewed evidence support that adherence to the Mediterranean diet during midlife was associated with 36%–46% greater likelihood of healthy ageing. Among the elderly, adherence to the Mediterranean diet was significantly associated with healthy ageing, while diets similar to that of the Mediterranean diet were associated with 269% greater likelihood of successful ageing and 33% reduction in mortality risk. Therefore, public health interventions aimed at promoting adherence to the Mediterranean diet, particularly among the elderly, may propagate healthy ageing and diminish the healthcare associated costs associated with age-related morbidity and mortality.

KEYWORDS

Mediterranean diet; healthy ageing; successful ageing; mortality

Introduction

Extended longevity is emerging as a concomitant opportunity and potential threat to individuals and wider societal interests in developed countries (Chang et al. 2019). Its impending effects are predominantly determined by whether individuals' extended lifespans are accompanied by the adverse effects of ageing, including progressive loss of physical, mental, and cognitive functions, ultimately leading to associated morbidity and fatality rates (Aunan et al. 2017; Chalan et al. 2015; Lopez-Otin et al. 2013; Mattson and Arumugam 2018). Recent epidemiological evidence reveals that changing age-related demographics have dramatically augmented the health burden of chronic non-communicable diseases and attributable disability (Engchuan et al. 2019; The Institute for Health Metrics and Evaluation (IHME)), accounting for 51.3% (95% Uncertainty Interval 48.5–53.9) of the total global disease burden among adults and incurring between 137.8 (128.9–148.3) to 265.9 (251.0–280.1) disability adjusted life years (DALYs) per 1000 adults in high and low sociodemographic index countries, respectively (Chang et al. 2019). With an ever-ageing population in developed countries, the investigation of the determinants of healthy ageing is an emerging public health priority for securing both citizens' quality of life and minimizing

healthcare associated costs. Such evidence is anticipated to best inform optimal and effective public health strategies, which are currently urgently pursued by governments worldwide (Chang et al. 2019), for promoting and propagating healthy (namely successful) ageing and, ultimately, diminish attributable healthcare costs.

Ageing entails convoluted biological pathways and processes (also known as the hallmarks of ageing), such as genomic instability and epigenetic alterations, mitochondrial dysfunction, altered intra- and intercellular sensing and communication, which lead to reductions in telomere length, mitotic alterations and dysfunctions, and ultimately cellular senescence and autophagy (Aunan et al. 2016; Barbosa et al. 2018; Grammatikakis et al. 2014; Lopez-Otin et al. 2013; Macedo et al. 2017; Victoria et al. 2017). Several non-modifiable sociodemographic factors (including level of education, marital status, employment status and/or household income, as well as social support networks) are documented as predictors of healthy ageing (Domenech-Abella et al. 2018; Engchuan et al. 2019; Noh et al. 2017). Of most public health interest, though, are modifiable lifestyle factors, including diet and physical activity, which may be altered via related interventions so as to facilitate healthy ageing. Diets rich in fruits and vegetables, with low glycaemic load and rich antioxidant content, such as most prominently the

Mediterranean diet, as well as the Okinawan and DASH diets, may enhance healthy ageing (Trichopoulou and Critselis 2004; Willcox et al. 2014). Specifically, the consumption of healthy dietary patterns, such as particularly that of the Mediterranean diet, has been associated with numerous health benefits and prevention of a variety of age-related disorders, such as cardiovascular disease (Grosso et al. 2017), metabolic syndrome, and cancers (Di Daniele et al. 2017), as well as all-cause mortality and longevity (Di Daniele et al. 2017; Trichopoulou and Critselis 2004). Most recently, particular constituents of the Mediterranean diet, such as olive oil which is rich in oleic acid and polyphenols (namely secoiridoids), have been shown to impact the biological pathways implicated in the hallmarks of ageing (Fernandez del Rio et al. 2016) and are associated with successful ageing in population-based investigations (Foscolou et al. 2019). Additionally, physical activity (Garatachea et al. 2015; Rebelo-Marques et al. 2018), as well as moderate caloric intake (Michan 2014) and optimal body weight (Perez et al. 2016), which constitute lifestyle behaviors proximally associated with adherence to the Mediterranean diet, are posited to also positively impact the hallmarks of ageing. However, to date, a comprehensive review of the current evidence regarding the potential impact of such lifestyle behaviors upon healthy ageing, so as to guide further related public health interventions, is lacking.

The present work sought to systematically review the current evidence arising from observational studies regarding the potential impact of adherence to the Mediterranean diet on healthy ageing among elder adults. In addition, it sought to identify current gaps in knowledge and provide insights for future directions for addressing this emerging field of public health concern.

Methods

To review the current evidence arising from prospective cohort studies regarding the potential impact of adherence to the Mediterranean diet on healthy ageing among elder adults we conducted a systematic literature search in MEDLINE and Web of Science Expanded Core Collection in the last 20 years (1 March 1999–1 March 2019) according to PRISMA reporting guidelines (Moher et al. 2015). The search query was conducted according to Boolean logic and included the following terms: ['Mediterranean diet*'] and ['ageing' OR 'aging'], ['healthy ageing' OR 'healthy aging'], and/or ['successful ageing' or 'successful aging']. Studies conducted in humans and published in English were eligible for review. The two authors independently reviewed all papers and decided whether should be included or not in this review; in the case of disagreement a third person assisted in the decision. Given the expanse of published studies, we decided a priori to focus on the observational studies of highest methodological quality anticipated to have the greatest impact, namely including population-based cross-sectional and prospective cohort studies. Of 509 initially retrieved unique items, 9 studies (including 2 cross-sectional and 7 prospective cohort studies) met inclusion criteria (Figure 1). The reviewed evidence is presented by

overall healthy ageing and/or individual health outcomes assessed, as defined according to 92 potential age-related disorders associated with population ageing (Chang et al. 2019). In particular, 5 studies assessed the impact of adherence to the Mediterranean diet upon healthy ageing and survival, while 4 studies evaluated its association with individual age-related outcomes including cognitive (2 studies) and functional (2 studies) decline. The characteristics of the studies selected, methodological tools and main findings are summarized in Tables 1 and 2, respectively.

Results

Mediterranean diet at midlife and healthy ageing

Two studies investigated the impact of adherence to the Mediterranean diet during midlife upon subsequent healthy ageing. Specifically, Assmann et al. (2018) investigated the association between adherence to the Mediterranean diet at midlife and subsequent healthy ageing. To this effect, data from 3012 participants of the French Supplémentation en Vitamines et Minéraux AntioXydants (SU.VI.MAX) study, aged 45–60 years at baseline (1994–1995) and free of major chronic diseases, were analyzed. Adherence to the Mediterranean diet was assessed based on the Literature-based Adherence Score to the Mediterranean Diet (LAMBD), calculated using repeated 24-hour dietary records. Healthy ageing (defined as absence of major chronic diseases (i.e. cancer, cardiovascular disease, or diabetes) depressive symptoms, and function-limiting pain, as well as good physical and cognitive functioning, independence in instrumental activities of daily living, good social functioning and self-perceived health), was subsequently assessed in 2007–2009. Following multivariable logistic regression analyses, higher adherence to the Mediterranean was associated with a greater likelihood of healthy ageing (Odd Ratio, OR LAMBD Tertile 3 vs Tertile 1: 1.36 [1.12; 1.65]). However, this association was found to be potentially mediated by metabolic health-related factors (Assmann et al. 2018).

Additionally, in the Nurse's Health Study (Samieri et al. 2013), the association between dietary patterns in midlife and prevalence of healthy aging were assessed employing a cross-sectional study design. In particular, 10,670 women (median age, 59 years) were assessed for health status 15 years later. Alternate Mediterranean diet scores were based on food-frequency questionnaire. Healthy aging was defined as survival to 70 years or older with maintenance of 4 health domains, including no major chronic diseases or major impairments in cognitive or physical function or mental health. Following adjustment for confounding effects, greater adherence to the Alternate Mediterranean diet induced 46% (CI, 17% to 83%) greater odds of healthy aging (Samieri et al. 2013).

Mediterranean diet among the elderly and healthy ageing

Three studies investigated the impact of adherence to the Mediterranean diet in the elderly upon healthy ageing and

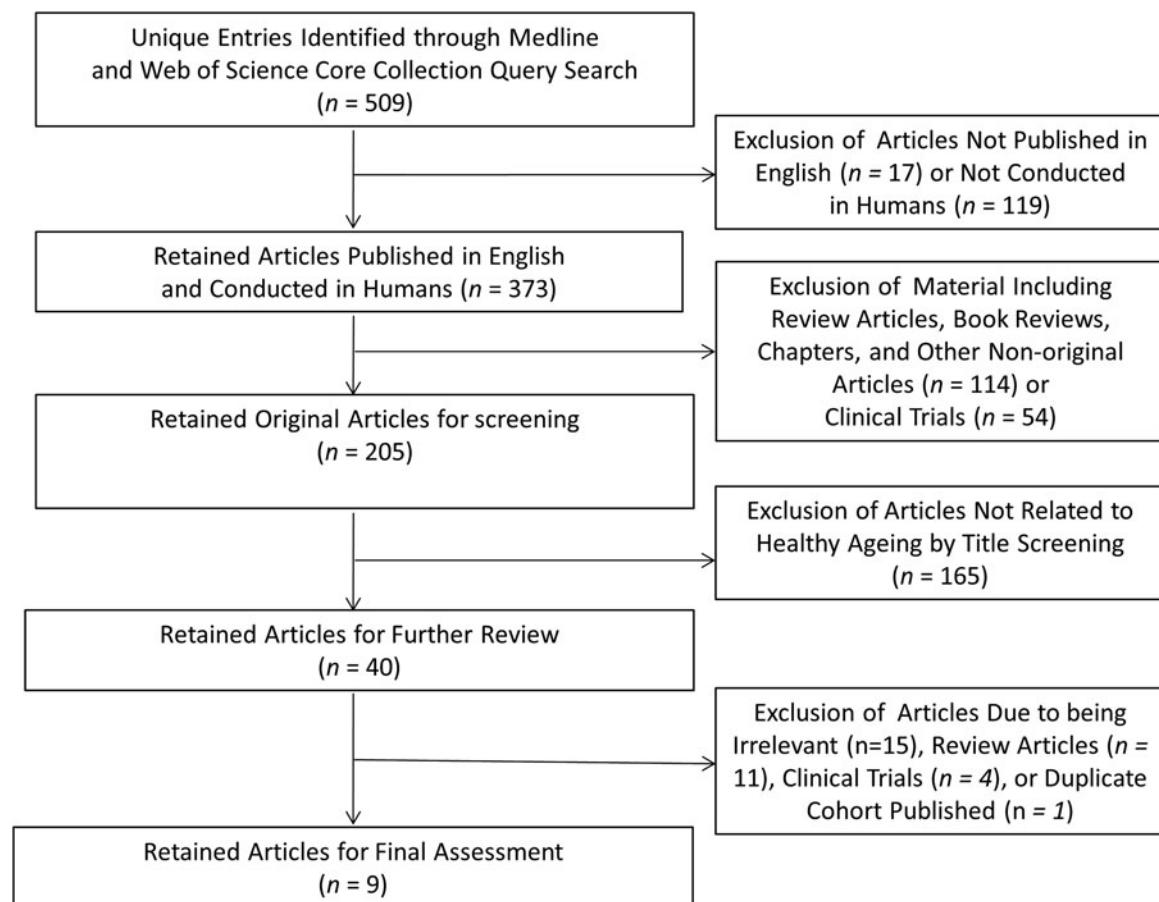


Figure 1. Search process used to select investigations regarding the impact of adherence to the Mediterranean diet and healthy ageing for the systematic review, March 1999–March 2019.

survival. In particular, Foscolou et al. (2018) evaluated life-style risk in relation to ageing in 3131 elderly individuals, ≥ 65 years of age, from 26 Mediterranean islands of 5 countries. Adherence to the Mediterranean diet was based on the MedDiet Score. The study findings revealed that adherence to the Mediterranean diet remained stable with increasing age ($p = 0.90$). In a subsequent combined analyses conducted in Greek adults aged >50 years old and enrolled in the ATTICA ($n = 1128$ adults from Athens metropolitan area) and the MEDiterranean Islands Study (MEDIS) ($n = 2221$ adults from various Greek islands and Mani) studies, the relation of between olive oil consumption and successful ageing was evaluated (Foscolou et al. 2019). Healthy ageing was measured using the validated Successful Aging Index (SAI). Following adjustment for age, sex, and smoking habits, exclusive olive oil intake (a hallmark of the Mediterranean diet), as compared to no use of olive oil, was significantly associated with healthy ageing ($p = 0.001$), particularly among those aged older than 70 years (Foscolou et al. 2019).

Additionally, in the Uppsala Longitudinal Study of Adult Men cohort study by Franzon et al. (2017), the association between Mediterranean diet adherence upon ageing and survival was assessed. In particular, of 1104 men (mean age of 71, range 69.4–74.1 years) investigated, 369 were evaluated for independent aging 16 years later (mean age 87, range

84.8–88.9 years). Adherence to a Mediterranean-like diet was assessed according to a modified Mediterranean Diet Score derived from 7-day food records. Independent aging was defined as a lack of dementia, a Mini-Mental State Examination score of 25 or greater, no institutionalization, independence in personal activities of daily living, and ability to walk outdoors alone. Adherence to a diet similar to that of the Mediterranean diet was associated with independent aging (OR = 2.69, 95% CI = 1.14–6.80), as well as survival (Franzon et al. 2017).

Finally, Knoop et al. similarly investigated the impact of the Mediterranean diet upon all-cause and cause-specific mortality in The Healthy Ageing: a Longitudinal study in Europe (HALE) population. This study included individuals enrolled in the Survey in Europe on Nutrition and the Elderly: a Concerned Action (SENECA) and the Finland, Italy, the Netherlands, Elderly (FINE) studies, encompassing 1507 and 832 otherwise apparently healthy men and women respectively, aged 70 to 90 years, from 11 European countries. Adherence to the Mediterranean diet was associated with a diminished risk of all-cause mortality (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.68–0.88), following adjustment for confounding factors including age, sex, years of education, and body mass index. Furthermore, lack of adherence was associated with a population attributable risk of 60% of all-cause deaths (Knoop et al. 2004).

Table 1. Characteristics of selected studies regarding the effect of adherence to the Mediterranean diet (MD) on healthy ageing (HA).

Author/year	Country	Study type	Population	Follow-up duration
MD in midlife and healthy ageing				
Assmann et al. 2018	France	Nested cohort (SU.VI.MAX trial)	3012 individuals (1578 M), aged 45–60 y at baseline	15 y (mean (\pm SD) follow-up time: 13.4 ± 0.5 y; mean age (\pm SD) at follow-up: 65.3 ± 0.5 y)
Samieri et al. 2013	USA	Cross-sectional (Nurse's Health Study)	10,670 women with no major chronic diseases at baseline (median age: 59 y)	15 y
MD in the elderly and healthy ageing				
Foscolou et al. 2019	Greece	Cross-sectional (ATTICA and MEDIS cohorts)	3349 individuals (52% M) from Attica Greece and 20 Greek islands, aged >50 y (mean (\pm SD) age: 69 ± 10 y)	NA
Franzon et al. 2017	Sweden	Cohort (Uppsala Longitudinal Study of Adult Men)	1104 men (mean age: 71 y, range 69.4–74.1 y)	16 y (mean age at follow-up: 87 y, range 84.8–88.9 y)
Knoops et al. 2004	Europe (11 European countries)	Cohort (The Healthy Ageing: a Longitudinal study in Europe (HALE Study))	2339 apparently healthy individuals (1507 M), aged 70–90 y	Mean follow-up time: 10 y, range: 8.9–10.5 y
MD and age-related outcomes				
Hill et al. 2018	Australia	Cross-sectional (Australian Women's Healthy Ageing Project)	111 women, aged 45–55 y at baseline	8 y
Tanaka et al. 2018	Italy	Cohort (InCHIANTI Study)	832 individuals, aged ≥ 65 y	18 y
Veronese et al. 2017	USA	Cohort (Osteoarthritis Initiative)	4358 community-dwelling participants (1831 M; mean age: 61.2 ± 9.1 y; range: 45–79 y)	–
Rahi et al. 2018	France	Cohort (French Three-City Study)	560 participants, aged ≥ 75 years	2 y

Adherence to the Mediterranean diet and age-related outcomes

Cognitive decline

Two studies investigated the association between adherence to the Mediterranean diet and subsequent cognitive decline. Specifically, Hill et al. (2018) investigated the impact of adherence to the Mediterranean diet upon the hallmark protein of neurocognitive decline, namely beta-amyloid. To this effect, a cross-sectional study was conducted among 111 participants of the Australian Women's Healthy Ageing Project. Adherence to the Mediterranean diet was assessed based on a validated food frequency questionnaire, while beta-amyloid deposition was measured by positron emission tomography. Following adjustment for covariates such as age, education, body mass index and cognition, as well as consideration of APOE- $\epsilon 4$ +/- status, no significant association between Mediterranean diet adherence and beta-amyloid deposition was detected (Hill et al. 2018).

Similarly, the study by Tanaka et al. (2018) evaluated the association between adherence to the Mediterranean diet and cognitive decline among 832 participants of the Invecchiare in Chianti (InCHIANTI) study in Italy. Cognitive performance was assessed using the Mini Mental State Examination (MMSE) every 2–3 years and up to 18 years follow-up. Adherence to the Mediterranean diet was based on a validated food frequency questionnaire. Participants with high adherence to the Mediterranean diet were less likely to manifest cognitive decline (OR = 0.48, 95% CI: 0.29–0.79).

Functional decline

Finally, two studies evaluated the impact of adherence to the Mediterranean diet upon subsequent functional decline. In the study by Veronese et al. (2017), the association between adherence to the Mediterranean diet and osteoarthritis was assessed. To this effect, 4358 community-dwelling participants (2527 females; mean age: 61.2 years) from the Osteoarthritis Initiative were enrolled. Adherence to the Mediterranean diet was evaluated by the validated Mediterranean diet score (aMED), and knee osteoarthritis was diagnosed based on both clinical and radiological findings. Higher adherence to the Mediterranean diet was associated with a lower prevalence of knee osteoarthritis (OR, 0.83; 95% CIs: 0.69–0.99) (Veronese et al. 2017).

Furthermore, the study by Rahi et al. (2018) evaluated the association between adherence to the Mediterranean diet and frailty among 560 participants aged ≥ 75 years of the population-based French Three-City Study. Adherence to the Mediterranean Diet was based on a food frequency questionnaire, while frailty was defined as having at least three of five modified Fried frailty criteria. Following 2 years of follow-up, multivariable logistic regression adjusted for sociodemographic and clinical covariates revealed that older adults adhering to the Mediterranean diet had a 68% frailty risk reduction (95% CI: 28–86%) (Rahi et al. 2018).

Discussion

The present systematic review of observational studies reveals that there exists consistent evidence supporting that

Table 2. Characteristics and main findings of selected studies for the effect of adherence to the Mediterranean diet (MD) on healthy ageing (HA).

Author/year	Methodology for assessing MD adherence	HA definition employed	Methodological tools for assessing HA or other age-related outcomes	Results
MD in midlife and healthy ageing Assmann et al. 2018	Literature-based Adherence Score to the Mediterranean Diet (LAMd), calculated using repeated 24-hour dietary records	HA defined as a dichotomous variable (i.e. meeting all criteria or not): (a) the absence of incident major chronic disease (cancer, cardiovascular disease or diabetes) during follow-up; limitations in instrumental activities of daily living (IADL), function-limiting pain, depressive symptomatology, and health-related limitations in social life; (b) the presence of: good physical and cognitive functioning and good overall self-perceived health.	CES-D (Center for Epidemiologic Studies Depression scale); DK-TMT (Delis-Kaplan Trail-making test); IADL (Instrumental activities of daily living); MMSE (Mini-Mental State Examination); RI-48 (Rappel Index-48 items); SF-36 (Medical Outcome Study Short Form-36); SPPB (Short Physical Performance Battery)	Higher MD adherence associated with greater likelihood of HA (Odd Ratio, OR LAMd Tertile 3 vs Tertile 1: 1.36 [1.12; 1.65])
Samieri et al. 2013	Semi-quantitative FFQ for calculating Alternative Healthy Eating Index-2010 (AHEI-2010) and Alternate Mediterranean diet (A-MeDi) scores	HA defined as survival to 70 years or older with maintenance of 4 health domains: free of 11 chronic diseases, with no impairment in cognition, no physical disabilities, and intact mental health	Biennial questionnaires for assessing incidence of 11 chronic diseases, SF-36 (Medical Outcome Study Short Form-36); Telephone Interview for Cognitive Status	Greater MD adherence to the Alternate Mediterranean diet associate with 46% (CI, 17% to 83%) greater odds of HA
MD in the elderly and healthy ageing Foscolou et al. 2019	FFQ, for calculating Mediterranean Diet Score (MedDiet Score)	Successful Ageing Index which encompasses health-related social, lifestyle, and clinical factors, including education, financial status, physical activity, BMI, depression, participation in social activities with friends and family, number of yearly excursions, total number of clinical CVD risk factors (i.e. history of hypertension, diabetes, hypercholesterolemia, obesity), and level of adherence to the Mediterranean diet	Successful Ageing Index (SAI)	Following adjustment for age, sex, and smoking habits, exclusive olive oil intake (a hallmark of the Mediterranean diet), as compared to no use of olive oil, was significantly associated with healthy ageing ($p = 0.001$)
Franzoni et al. 2017	7-day food record and modified Mediterranean Diet Score (mMDS) for determining the degree of adherence to a Mediterranean-like diet	Independent ageing defined as lack of diagnosed dementia, a Mini-Mental State Examination (MMSE) score of 25 or greater, not being institutionalized, independence in ADLs, and ability to walk outdoors alone at age 87 (ULSAM-6)	MMSE (Mini-Mental State Examination) and ULSAM-6	Adherence to a diet similar to MD was associated with independent ageing (OR = 2.69, 95% CI = 1.14–6.80)
Knoops et al. 2004	Dietary history based on interview and food record, for calculating the modified Mediterranean Diet Score (MDS)	All-cause mortality and lifestyle score calculated by adding the individual scores for diet, physical activity level, smoking status, and alcohol intake.	10-year mortality and lifestyle score	Following adjustment for age, sex, years of education, and BMI, MD adherence was associated with a diminished risk of all-cause mortality (HR: 0.77; 95% CI: 0.68–0.88),

(continued)

Table 2. Continued.

Author/year	Methodology for assessing MD adherence	HA definition employed	Methodological tools for assessing HA or other age-related outcomes	Results
MD and age-related outcomes				
Hill et al. 2018	Dietary Questionnaire for Epidemiological Studies Version 2 (DQES), for calculating and MD adherence based on modified MD score (Sofi et al. 2010)	NA	Beta-amyloid deposition was measured using positron emission tomography standardized uptake value ratios	Following adjustment for covariates such as age, education, body mass index and cognition, as well as consideration of APOE-ε4 +/- status, no significant association between Mediterranean diet adherence and beta-amyloid deposition High MD adherence was inversely associated with cognitive decline (OR = 0.48, 95% CI: 0.29–0.79) Higher MD adherence was associated with a lower prevalence of knee osteoarthritis (OR, 0.83; 95% CI: 0.69–0.99)
Tanaka et al. 2018	European Prospective Investigation on Cancer and Nutrition FFQ, for calculating the Mediterranean Diet Score (MDS)	NA	MMSE (Mini Mental State Examination)	
Veronese et al. 2017	Block Brief 2000 FFQ, for calculating MD adherence based on Mediterranean diet score (MedDietScore)	NA	Knee osteoarthritis defined as the combination in the clinical reporting and assessment of pain and stiffness, and radiographical osteoarthritis on fixed flexion radiograph, including presence of tibiofemoral osteophytes (Osteoarthritis Research Society International atlas grades 1–3, clinical center reading)	
Rahi et al. 2018	Semi-quantitative FFQ for calculating Mediterranean Diet Score (MDS)	NA	Frailty defined as having at least three out of the following five slightly modified Fried frailty criteria: involuntary weight loss, exhaustion, slowness, weakness and low physical activity.	Following adjustment for sociodemographic and clinical covariates, older adults adhering to the Mediterranean diet had a 68% frailty risk reduction (95% CI: 28–86%)

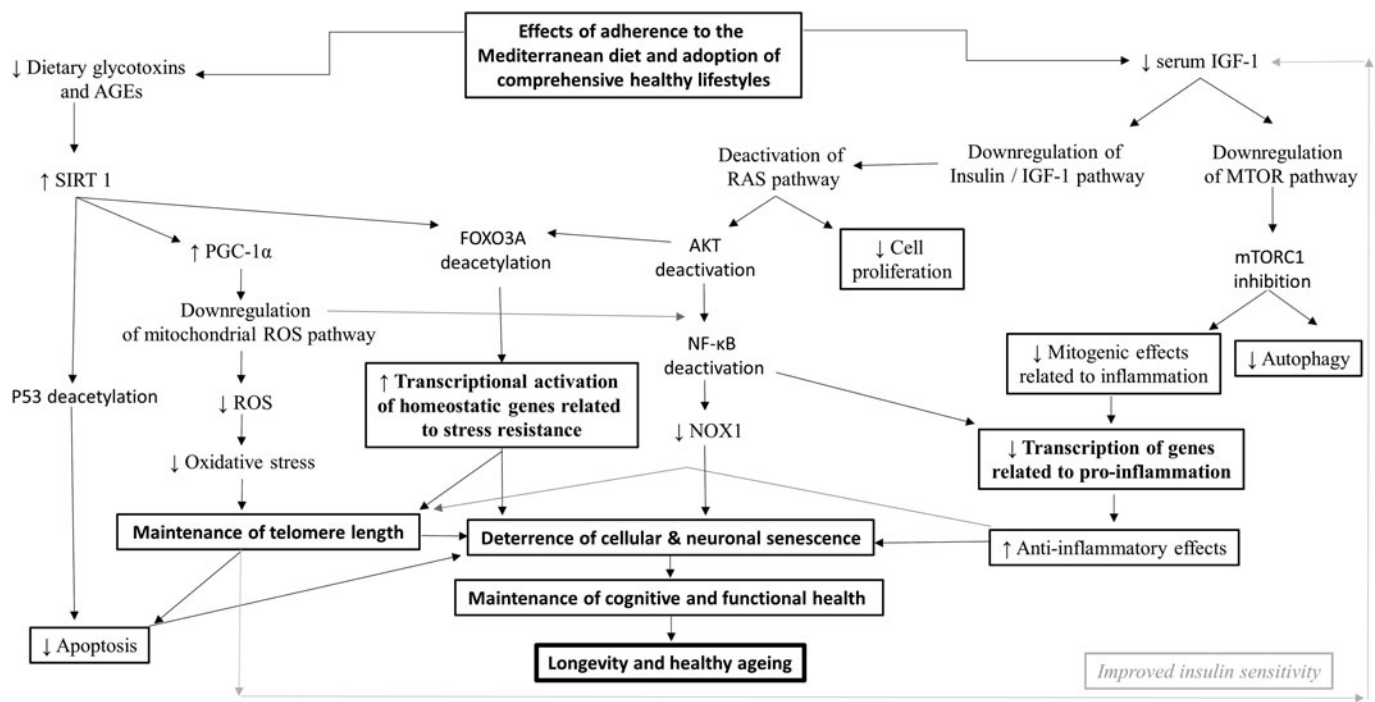


Figure 2. Potential mechanisms and pathways linking adherence to the Mediterranean diet and healthy ageing. An overview of the mechanisms and nutrient-sensing pathways which modulate healthy ageing are depicted. In brief, adherence to the Mediterranean diet most often entails diminished ingestion of dietary glycotoxins and production of advanced glycation end-products (AGEs), which activate Sirtuin 1 (SIRT 1); subsequent downregulation of the mitochondrial reactive oxygen species (ROS) pathway leads to deterrence of telomere attrition and diminished cellular apoptosis and death. Concomitantly, adherence to the Mediterranean diet induces lower serum IGF-1 levels, which downregulate several nutrient-sensing pathways, including the MTOR and Insulin/IGF-1 pathways. In particular, MTOR pathway downregulations leads to an enhanced anti-inflammatory intracellular environment and diminished cellular autophagy. In parallel, downregulation of the Insulin/IGF-1 pathway induces consequent deactivation of the AKT and NF- κ B pathways, enhancing anti-inflammatory effects and deterring cellular and/or neuronal senescence. The constellation of the aforementioned pathways favor the deterrence of cellular and neuronal ageing, facilitating cognitive and functional health, and ultimately preserve healthy ageing.

adherence to the Mediterranean diet and healthy ageing. Specifically, adherence to the Mediterranean diet during midlife was associated with a 36% to 46% greater likelihood of healthy ageing. Similarly, among the elderly, adherence to the Mediterranean diet, and particularly the exclusive use of olive oil, was significantly associated with healthy ageing, while diets even similar to that of the Mediterranean diet were associated with 269% greater likelihood of successful ageing. Such practices were also associated with a 33% reduction in mortality risk in this particular age group. In relation to age-related outcomes, disparate findings exist, as the retrieved evidence supports that adherence to the Mediterranean diet protects from overall cognitive decline by 52%, albeit not from beta-amyloid deposition per se. Finally, in relation the impact of the Mediterranean diet upon functional decline, evidence arising from the reviewed investigations agree that the adoption of such dietary patterns notably reduce the risk of frailty by 68%, as well as osteoarthritis. As of such, there is sufficient evidence to support that public health interventions aimed at promoting adherence to the Mediterranean diet, particularly among the elderly, may propagate healthy ageing and, ultimately, potentially diminish the healthcare associated costs associated with age-related morbidity and mortality.

Ageing entails multiple biological pathways and processes, including genomic instability and epigenetic alterations, mitochondrial dysfunction, altered intra- and intercellular sensing and communication. Based on preliminary pathways

previously reviewed for preserving cognitive (Knight et al. 2016) and other age-related functions associated with healthy ageing (Vasto et al. 2014), as well as the present review findings, the potential mechanisms and pathways which may underlie the association between adherence to the Mediterranean diet and healthy ageing are presented in Figure 2. These cascades result in mitotic alterations and dysfunctions, cellular senescence, and attrition in telomere length (Aunan et al. 2016; Barbosa et al. 2018; Grammatikakis et al. 2014; Lopez-Otin et al. 2013; Macedo et al. 2017; Victoria et al. 2017). As heterochromatic repeat chromosomal regions, telomeres are revered as a reliable hallmark of biological ageing. Telomere shortening may result from the diminishment and/or absence in telomerase activity, while preliminary findings in both animal models and humans exhibit that a genetic predisposition to telomere shortening advanced biological ageing is associated with several single nucleotide polymorphisms, including polymorphisms of the TERC gene such as rs10936599, rs12696304, rs16847897 and rs3772190 (Michalek et al. 2017; Scarabino et al. 2019).

Telomere shortening may be deterred via lifestyle factors, such as healthy diet, physical activity and optimal weight maintenance. In particular, the consumption of antioxidant rich diets with plentiful fruits and vegetables are associated with longer telomere length (Freitas-Simoes et al. 2016; Rafie et al. 2017). Moreover, adherence to the Mediterranean diet, and particularly consumption of olive

oil and fish, has been long established as a protective factor for securing telomere size (Corina et al. 2019; Davinelli et al. 2019; Freitas-Simoes et al. 2016), particularly as subjects consuming >30 mL olive oil/day have been observed to have longer telomere length than their counterparts with lower consumption within the context of the CARDIOPREV Study (Corina et al. 2019). It is upheld that the Mediterranean diet, considered as a complex exposome consisting of numerous nutrients and phytochemicals which reduce inflammation and oxidative stress, may deter telomere attrition (Davinelli et al. 2019). Preliminary findings suggest that such effects are induced by a reduction in the levels of 8-hydroxy-2'-deoxyguanosine, variation in DNA repair gene expression, and subsequent adverse impact on telomere length (Del Bo et al. 2019). Adherence to the Mediterranean diet entails higher vitamin E levels which are associated with longer telomere length potentially via diminished levels of glutathione peroxidase activity (Corina et al. 2019). However, to date, the precise underlying pathophysiological mechanisms by which adherence to the Mediterranean diet may ultimately deter age-related disorders and facilitate healthy ageing through telomere maintenance remain to be elucidated (Davinelli et al. 2019), mandating further related observational studies entailing repeated measures and/or randomized clinical trials (Del Bo et al. 2019; Freitas-Simoes et al. 2016; Rafie et al. 2017). Even so, in recognition of the emerging need to promote dietary patterns (inclusive but not restricted to those similar to the Mediterranean diet) which may propagate healthy ageing, initially scientific societies (namely the American Heart Association (Krauss et al. 1996)) and subsequently international public health and academic organizations dedicated concerted efforts so as to compile uniform food-based dietary guidelines and nutrient intake recommendations for older persons (namely the WHO Guidelines 'Keep fit for life: Meeting the nutritional needs of older persons') for securing healthy ageing, particularly encompassing the prevention of chronic non-communicable diseases and promotion of physical activity (World Health Organization 2002).

However, in order to optimize the generalizability, as well as clinical and public health applications, of such investigations which may further inform and guide such public health interventions, it is necessary that healthy ageing is foremost clearly defined, operationalized, and measured based on common criteria agreed upon by members of the international scientific community. As displayed by the present review of the current evidence, healthy and/or successful ageing are apparently often not uniformly defined and/or measured by common approaches and methods between studies, impeding the comparability and/or generalizability of research findings. A recent review of 50 epidemiological studies from 23 countries regarding measurement methods applied for the assessment of healthy ageing revealed the disparate approaches and measurement methods currently applied for assessing healthy ageing. Specifically, the investigation revealed that less than half (19/50) of reviewed studies applied Rowe and Kahn's three standards for assessing healthy aging. Furthermore, approximately two thirds of

studies measured physical capabilities by activities of daily living (37/50) and cognitive function (33/50). While approximately half (26/50) of the studies assessed metabolic and physiological health, this was mainly confined to self-reported absence of diseases. Diverse scales were employed for assessing psychological well-being among half (24/50) of the studies reviewed. Finally, health behaviors were taken into account solely by 3 of the studies reviewed (Lu et al. 2018).

Additionally to the non-modifiable sociodemographic factors associated with health ageing (including level of education, marital status, employment status and/or household income, as well as social support networks) (Domenech-Abella et al. 2018; Engchuan et al. 2019; Noh et al. 2017), it is imperative that modifiable health behaviors are considered in future measurement methods tailored to comprehensively assess healthy ageing. Specifically, there is ample evidence that healthy dietary patterns such as that of the Mediterranean diet prevent the onset and progression of several age-related disorders, including cardiovascular disease (Grosso et al. 2017), metabolic syndrome, and several cancers (Di Daniele et al. 2017), as well as all-cause mortality and longevity (Di Daniele et al. 2017; Trichopoulou and Critselis 2004). The present review findings further support that adherence to the Mediterranean diet, in either midlife or later years, is associated with healthy ageing, as well as the prevention of overall cognitive and functional decline. Similar investigations ought to further investigate similar independent or mediating effects based on preliminary findings regarding physical activity (Garatachea et al. 2015; Rebelo-Marques et al. 2018), caloric intake (Michan 2014) and maintenance of optimal body weight (Perez et al. 2016). Based on the above, the comprehensive assessment of the constellation of such health behaviors are anticipated to provide essential insights regarding the epigenetic effects and pathways implicated in the hallmarks of ageing.

In tandem, all of the above highlight the urgent need for developing comprehensive uniform operational definitions of healthy ageing and measurement methods so as allow for the optimal potential of this emerging research field to be fully achieved.

Future outlook

Most recently, based on the current gaps in knowledge and disparate measurement methods for assessing healthy ageing, the international Ageing Trajectories of Health: Longitudinal Opportunities and Synergies (ATHLOS) project (European Union's Horizon 2020 research and innovation program, grant agreement no. 635316) was established so as to achieve a better understanding of ageing, including the development of a novel operationalized definition of healthy ageing, as well as its determinants. Furthermore, this initiative will develop a novel comprehensive single metric of healthy ageing, based on the largest longitudinal prospective population-based inception cohort studies worldwide and the agreement between several statistical methodologies employed. It is anticipated that the above state-of-the-art

innovations will best inform the effective study design and implementation of future related investigations and, ultimately, guide future public health interventions for optimizing healthy ageing in Europe and beyond.

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