

# A systematic overview of the scientific literature on the association between Mediterranean Diet and the Stroke prevention

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## Abstract

**Background.** stroke is the most common cardiovascular disorder after heart disease and one of the major causes of death and disability. Mediterranean diet has proven to be an effective means to prevent cardiovascular diseases and may contribute to the prevention of stroke.

This overview aims to analyze all reviews that examine the association between Mediterranean diet pattern and stroke.

**Methods.** we conducted a literature search on PubMed and Scopus databases, using the keywords “Mediterranean diet” and “Stroke”. All studies were selected evaluating the association between the Mediterranean diet and the prevention of stroke and only systematic reviews, meta-analysis and narrative reviews were included.

**Results.** 25 eligible articles were included (16 narrative reviews, 9 systematic reviews, 6 systematic reviews with meta-analyses). The authors stated that Mediterranean diet may be a useful means of preventing stroke, especially the 6 meta-analyses highlighted that high adherence to Mediterranean diet was protective against stroke, with a relative risk ranging from 0,64 (95% CI 0,48-0,88) to 0,90 (95% CI 0,87-0,93). Moderate adherence has not shown significant results.

**Conclusions.** a high adherence to the Mediterranean diet is inversely associated with stroke risk, and can modify the costs of its management, therefore the prevention policies should implement adherence to this healthy diet. *Clin Ter 2019; 170(5):e396-408. doi: 10.7417/CT.2019.2166*

**Key words:** Stroke, Ictus, Mediterranean diet, dietary habits, healthy diet, prevention, overview, systematic

## Introduction

Annually, 15 million people worldwide suffer a stroke. Of these, 5 million die and another 5 million are left permanently disabled, placing a burden on family and community (1). According to WHO, stroke is the second leading cause of death for people above the age of 60 years, and the fifth leading cause in people aged 15 to 59 years old (2). Worldwide, China has one of the highest rates of mortality

(19,9% of all deaths in China), along with Africa and parts of South America (3).

The major risk factors for stroke are similar to those for coronary heart disease (CHD), with high blood pressure, the most important modifiable cause of stroke, and tobacco. Other modifiable risk factors include underlying heart disease, diabetes, high blood lipids, unhealthy diet and high salt intake.

The incidence of stroke is declining in many developed countries, largely as a result of better control of high blood pressure, and reduced levels of smoking, but it has doubled in low- and middle-income countries (4). However, the absolute number of strokes continues to increase because of the ageing population: WHO predicts that disability-adjusted life years (DALYs) lost to stroke (a measure of the burden of disease) will rise from 38 million in 1990 to 61 million in 2020 (2).

The estimated direct and indirect cost of stroke in the US for 2010 was \$ 73,7 billion and in Europe was approximately € 64.1 billion (5).

Given these dismal statistics and the high cost of treatment of stroke, high priority should be accorded to preventive strategies and the Mediterranean diet may be among these.

There is substantial evidence of the long-term beneficial effects of the Mediterranean diet on health. In prospective cohort studies, several versions of Mediterranean diet scores have been associated with reduced total mortality (6–10) and lower risk of cardiovascular disease (CVD) (11–13), cancer (14, 15), and neurodegenerative diseases (16) in apparently healthy populations.

Populations that follow the Mediterranean diet pattern show a 50% lower rate of cardiovascular mortality due to cardiovascular diseases and show highest longevity (17).

Living in a Mediterranean way means having healthy food but also adopting a specific way of life made of conviviality, traditions and daily moderate physical exercise.

This is probably the reason for a success began 60 years ago when Ancel Keys, first disclosed the virtues of the Mediterranean Diet, thought to have found the elixir of life in the Cilento region, in Southern Italy.

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Several authors recognize that this diet is based on the following dietetic pattern (18): high intake of vegetables, pulses (beans, lentils etc.), fruit and cereals, high consumption of olive oil (as the prevalent visible fat), medium-low intake of dairy produces (mainly yogurt and cheese), a moderate intake of wine. The intake of saturated animal fats is relatively low, and there is a moderate fish consumption (depending on the proximity to the sea), which furnishes enough provision of polyunsaturated fats, thus making it a low-glycemic-index diet (19).

Consumption of fatty acids as a percentage of total energy intake, protein, the MUFA to SFA ratio and fibers, vitamins C and E, minerals including selenium and potassium, folate,  $\beta$ -carotene, antioxidant or phytosterol content may be useful nutrients to consider in defining the diet, as these nutrients are consistently implicated as combining for anti-CVD, anti-cancer, anti-aging effects and preventing cognitive decline (20-24).

Because this is a palatable dietary pattern, adherence to a Mediterranean-style diet can be easily achieved by the general population in and outside the Mediterranean basin (25,26). However, the traditional MD (Mediterranean diet) is now progressively eroding due to the widespread dissemination of the Western-type economy, urban and technology-driven culture, as well as the globalization of food production and consumption, related to the homogenization of food behaviors in the modern era.

In the latest years, there has been a significant change in dietary habits and physical activity levels worldwide as a result of industrialization, urbanization and globalization, bringing the increase of diseases and conditions linked to an unhealthy diet including obesity, diabetes, cardiovascular diseases and stroke (1,2) that ranked third as the leading global causes of disability-adjusted years according to the global burden of disease estimates for 2010 (27).

The projections of mortality from CVD for 2030 are dismal (28,29), highlighting the need for preventive strategies as a public health priority.

The growing impact of chronic degenerative pathologies in high income countries requires and pushes towards the development of new preventive strategies to reduce the incidence and prevalence of these diseases (30).

Recently, the relevance of overall high-quality food patterns, rather than the focus on single nutrients and foods, has emerged as a powerful paradigm to address the inherent complexity of dietary exposures and to assess their potential CVD preventive effects.

In this context, lifestyle changes and especially a high-quality diet related to the Mediterranean diet are largely considered in the scientific literature as the most important factors for CVD prevention. The adherence to the Mediterranean diet has been extensively reported to be associated with a favorable health outcome and a better quality of life. The implementation of a Mediterranean dietary pattern may lead to the prevention of degenerative pathologies and to an improvement in life expectancy, a net gain in health and a reduction in total lifetime costs (30,31).

This overview aims to analyze all reviews that examine the association between Mediterranean diet pattern and stroke to obtain an extensive but specific point of view

based on the scientific production and to minimize the bias concerning the low quality studies.

## Materials and Methods

### Protocol and registration

The protocol of this review was registered prospectively with PROSPERO, code CRD42018095736.

### Identification of relevant studies

A medical literature review was carried out on PubMed and Scopus databases using the keywords “Mediterranean diet”, “Stroke” with the Boolean operator AND.

The limits applied refer to the language of the articles (English, Spanish, Italian) but not to the year of publication. When duplicate or repeated publications were encountered in the database search, the papers, when eligible, were considered only once. The search ended in January 2018.

### Study selection and eligibility criteria

For the analysis, all studies were selected independently by two researchers evaluating the association between the Mediterranean diet and the prevention of stroke. All process was performed according to the PRISMA statement (Preferred Reporting Items Systematic Reviews and Meta-Analyses), to provide univocal and comparable data, as shown in the flow chart (Fig.1).

Eligibility criteria based on the PICOS (population, intervention/exposure, comparator group, outcome and study design) were used as follows: Population: people at risk of cardiovascular events or not; Intervention/Exposure: adherence to the Mediterranean diet; Comparator group: population that doesn't adhere to the Mediterranean diet or follow alternatives dietary patterns; Outcomes: stroke prevention; Study design: narrative reviews, systematic reviews and meta-analyses.

Articles were excluded if studies were not pertaining to the topic “Mediterranean diet and Stroke”. All duplicate records were excluded from medical databases.

### Data extraction and quality assessment

All publications were analyzed by two different researchers who independently reviewed the papers to identify relevant information and to extract data. Disagreements about data extraction were solved with a third researcher.

The quality of narrative reviews were assessed using INSA (International Narrative Systematic Assessment) tool (32) (Table 1), while systematic reviews and meta-analysis were evaluated using AMSTAR (Assessment of Multiple Systematic Reviews) (33) (Tables 2-3).

All the studies were reviewed by two different researchers to assess the quality. Disagreements about quality were solved with a third researcher.

## Results

### Identification of studies

A total of 308 articles were retrieved: 110 from PubMed search and 198 articles from Scopus search.

Articles were subjected to an accurate screening of both the title and the abstract from the two search engines separately and to the removal of duplicates in each database.

As shown in the flow chart (Figure 1), of the 308 articles, 218 were removed, because they were not relevant or not met the inclusion criteria, and 48 were duplicates. Finally, 42 articles were assessed for eligibility: all full texts were examined; at the end of the evaluation, seventeen articles with no pertinent full text were excluded.

At the end of the selection process, only 25 articles met the pre-determined criteria: 16 narrative reviews (34-49), 9 systematic reviews (20,50-57), of which 6 performed also the meta-analysis (20, 50,54-57).

### Narrative Reviews

The narrative reviews that were included in this study, focused on prevention (primary and secondary) of stroke, mainly supporting nutrition as possible strategy. They were analyzed single foods, nutrients or dietary pattern (including Mediterranean diet) that could have a harmful or beneficial role against stroke (Table 1).

### Systematic Reviews

All systematic reviews were aimed to evaluate the association between the Mediterranean diet or dietary patterns, that also included the Mediterranean diet, and stroke or CVD (including stroke).

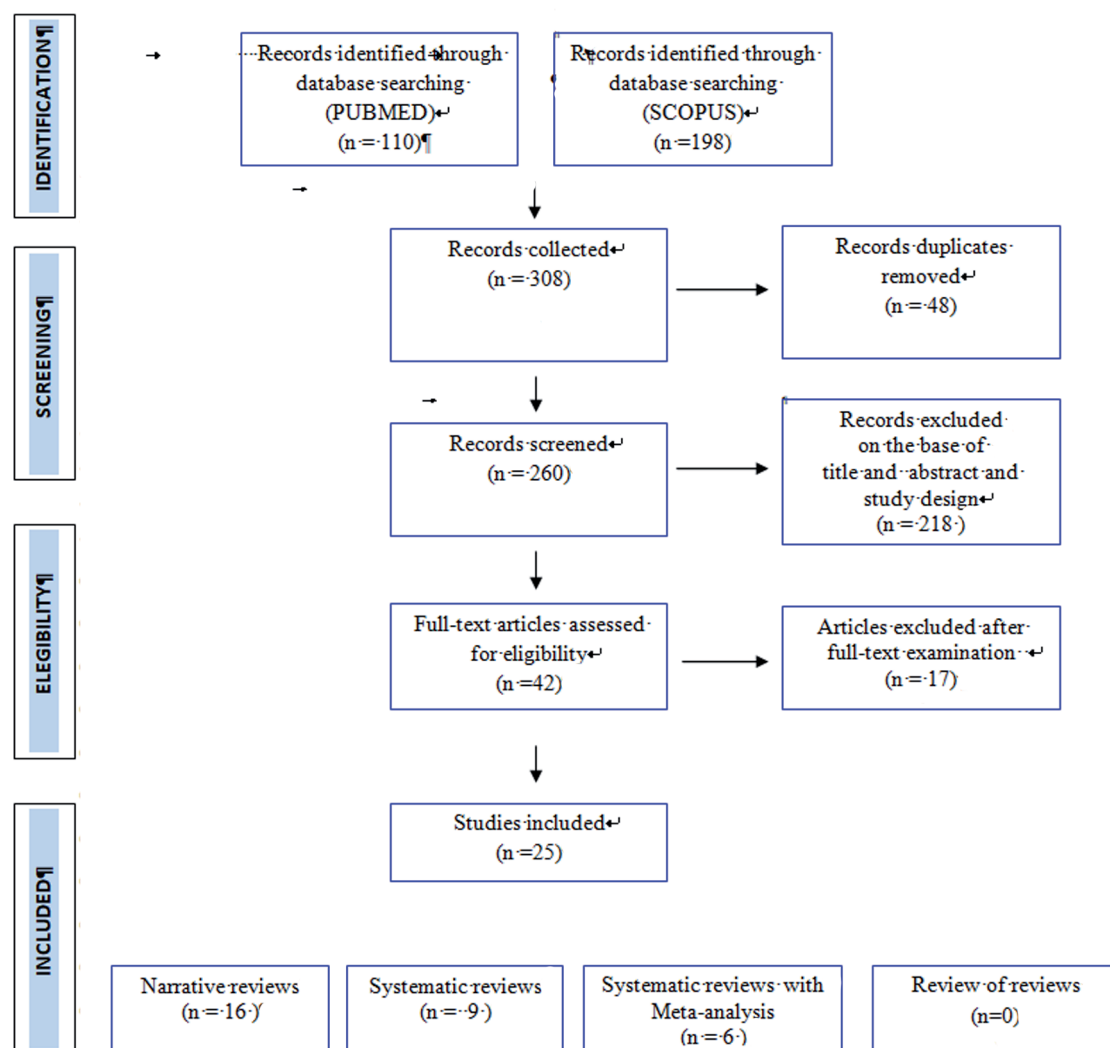


Fig.1.Flow diagram of the literature search results conducted up to January 2018

Table 1. Characteristics of the included narrative reviews and INSA Tool

Authors and Year of Publication	Aims	Authors' Conclusions	INSA Tool
Apostolopoulou et al, 2012 <sup>34</sup>	To provide a global approach on how diet can influence the risk of stroke and especially the nutritional influence on lipid profile and vessel disease and the role of dietary modification in the secondary stroke prevention	The importance of salt restriction, DASH and a Mediterranean diet low in saturated and high in polyunsaturated fats, and the management of obesity would seem to be the most important dietary priorities of a holistic national intervention	6
Ayuso et al, 2017 <sup>45</sup>	To review several dietary bioactive compounds from studies that have obtained promising results decreasing cerebral damage in models of cerebral ischemia	Since many studies evidenced that the presence of dietary bioactive compounds in the system is neuroprotective before stroke occurs reducing brain injury, the authors propose those compounds in order to apply an advanced neuroprotection to protect the brain of high-risk patients before damage occurs.	6
Boden-Albala et al, 2015 <sup>43</sup>	To discuss available clinical research findings reporting on the relationship among diet/ dietary patterns, cardiovascular disease, and risk of stroke and assess challenges, limitations, and controversies, and address future research directions	Research has yet to determine a dietary intervention to reduce risk of stroke, incidence, and mortality within the context of the USA. New strategic directions must be implemented using multi-level approaches that incorporate research, clinical practice, public health, communities, and advocacy to better predict and prevent stroke incidence	6
Dearborn et al, 2015 <sup>36</sup>	To summarize the knowledges about dietary patterns and secondary stroke prevention, make some interim recommendations and discuss how future work might help develop the potential for this therapeutic approach	A healthy diet may have a similar effect size of statins for secondary prevention but is hardly mentioned during hospital admissions and clinic follow-up visits for stroke patients. This may be because there is no direct research data to show that any specific diet is more effective than another in secondary stroke prevention	5
Demarin et al, 2011 <sup>37</sup>	To discuss the beneficial and preventive role of Mediterranean diet in the occurrence of cardiovascular diseases, chronic neurodegenerative diseases and neoplasms, obesity and diabetes	Greater adherence to Mediterranean diet is associated with significant reduction in overall mortality, mortality from cardiovascular diseases and stroke, incidence of or mortality from cancer, and incidence of Parkinson's disease and Alzheimer's disease and mild cognitive impairment	3
Hankey G. et al, 2012 <sup>44</sup>	To examine the evidence linking nutrition and diet to the risk of stroke	Less reliable evidence suggests that stroke can be prevented by diets that are prudent, aligned to the Mediterranean or DASH (Dietary Approaches to Stop Hypertension) diets, low in salt and added sugars, high in potassium, and meet, but do not exceed, energy requirements. Further research is needed to improve the quality of evidence relating to the association of many nutrients, foods, and dietary patterns with stroke risk	7
Isabel et al, 2016 <sup>48</sup>	To review the evidence-based treatments for secondary prevention after ischemic or hemorrhagic stroke	Over the past 50 years, there was a development of therapies of stroke with proven efficacy, including antihypertensive therapy, antiplatelet therapy, VKAs and NOACs, statins, carotid endarterectomy and carotid stenting. Because compliance with secondary stroke prevention strategies is not optimal in routine clinical practice, guideline dissemination must be coupled with effective implementation strategies to render more effective the implementation of results from RCTs into clinical practice	6
Jackson et al, 2016 <sup>49</sup>	To describes how engaging in physical activity and cognitive activities and adhering to a Mediterranean style diet promote brain health	The capacity for plasticity of the older adult brain is built up through engaging with physical and cognitive activities and adhering to a diet rich in healthy fats and plant phytochemicals so that the clinical manifestations of ageing and neurodegenerative disease are kept at bay for longer. A three-pronged approach including a Mediterranean Diet intervention may prove to be even more beneficial, but has yet to be developed.	4
Lakkur and Judd 2015 <sup>35</sup>	To review the evidence for a Mediterranean style diet, and the foods that characterize this diet in stroke prevention	There is evidence supporting an association between the Mediterranean diet pattern (both individual foods and full pattern) and decreased stroke risk	6
Martinez-Gonzalez and Martin-Calvo 2016 <sup>47</sup>	To update the available evidence of the effects of the Mediterranean diet and lifestyle on health	All the recent observational studies support impressive benefits for the Mediterranean Diet, but, beyond diet, the evidence is largely missing for other aspects of the Mediterranean lifestyle, notably for a physically active lifestyle. In September 2013 a new Spanish large primary prevention trial was launched, labeled PREDIMED-PLUS and will allow the assessment of the long-term cardiovascular effects of a full package of Mediterranean lifestyles, which goes beyond the dietary pattern ( results in 2021)	7

(following table)

Niewada and Michel 2016 <sup>46</sup>	To summarize recent findings on the impact of lifestyle modifications on first or recurrent stroke risk	Lifestyle modifications should address a multiple cardiovascular risk factors to effectively reduce stroke risk and professionals should focus both on medical and lifestyle modifications to decrease strokes and other vascular diseases	6
Spence J. 2006 <sup>38</sup>	To discuss current issues that include the intake of animal fat and cholesterol, the Cretan Mediterranean diet, the failure of most studies to show benefit of supplements with antioxidant vitamins such as vitamins E and C, and the current controversy over failure of recent clinical trials to show reduction of stroke and other cardiovascular events by lowering plasma total homocysteine with folate, B6, and B12.	Patients at risk of stroke should consume a Cretan Mediterranean diet, avoid egg yolks, eat less animal flesh than do most North Americans, and require higher doses of B12, and in the future they may benefit from improved therapies to lower levels of total homocysteine	5
Spence J. 2010 <sup>39</sup>	To discuss recent advances in secondary ischemic stroke prevention	Secondary stroke prevention is remarkably effective, having the potential to reduce the risk of recurrent stroke by ~80–90%. New antiplatelet agents and anticoagulants offer promise of better preventative therapy than currently exists. Carotid endarterectomy and stenting can no longer be regarded as appropriate for asymptomatic carotid stenosis, except in a small proportion of highly selected cases	7
Spence J. 2013 <sup>40</sup>	To discuss lifestyle change, blood pressure control, lipid-lowering therapy, appropriate use of antiplatelet agents and anticoagulants, appropriate carotid endarterectomy or stenting, and new approach called “treating arteries instead of targeting risk factors”	Smoking cessation, a Mediterranean diet, blood pressure control individualized to the cause of the hypertension, appropriate use of antiplatelet agents and anticoagulants, and appropriate endarterectomy are all important in stroke prevention	6
Spence J. 2017 <sup>41</sup>	To discuss the harm from dietary cholesterol and egg yolk, the Cretan Mediterranean diet, the interaction of the intestinal microbiome, impaired renal function and diet, undiagnosed metabolic B12 deficiency, and B vitamins for stroke prevention	The Mediterranean diet should be adopted by patients with stroke or at risk of stroke, instead red meat and egg yolk should be avoided, particularly by patients with impaired renal function, and all patients with stroke or threatened stroke with metabolic B12 deficiency/high homocysteine should be treated.	4
Spence J. 2017 <sup>42</sup>	To update the 2013 review <sup>40</sup>	The key to preventing recurrent stroke is to identify the cause of the initial event so that therapy can be individualized to the patient. The recurrent stroke could be reduced even more with the recent advances in hypertension, nutrition, anticoagulation, antiplatelet therapy, intracranial stenosis, and lipid-lowering therapy	5

Reviews carried out by Kontogianni and Panagiotakos (50), Sherzai (51), Ding (52), and Faroughi (53), Rosato (54), Grosso (55), had the aim to linking food groups or dietary patterns (including Mediterranean dietary pattern) with stroke or CVD in general and assessed the preventive effects in terms of incidence and mortality; while the reviews carried out by Sofi (20), Psaltopoulou (56) and Liyanage (57) investigated the health benefits of adherence to the Mediterranean Diet (Table 2).

Moreover Sofi (20), Kontogianni and Panagiotakos (50), Psaltopoulou (56), Grosso (55), Liyanage (57) assessed the quality of the individual studies included in their reviews.

The Kontogianni and Panagiotakos' review (50) included observational studies (i.e. prospective cohorts and case-control studies) and randomized clinical trials (RCT) that examined the relationship between dietary patterns as exposure and stroke as the main outcome. Cross-sectional studies were excluded, due to prone to reverse causality, as well as studies in subjects with already established CVD. In addition to the Mediterranean dietary pattern, they also assessed Prudent diet, DASH diet, “westernized” patterns based on animal foods, sweets and fats.

They considered the meta-analysis by Psaltopoulou *et al.* (56) that stated that the high adherence to the Mediterranean dietary pattern was associated with reduced risk of stroke (pooled effect estimate=0.71; 95% CI 0.57-0.89). However, the protective effect concerning stroke was only marginal when moderate vs. low adherence to the traditional Mediterranean diet was examined (pooled effect estimate = 0.90; 95% CI 0.81-1.00). Moreover, they mentioned the Greek EPIC (European Prospective Investigation into Cancer and Nutrition) study (58), that included 23,601 participants that were followed-up for a median period of 10.6 years. Participants in the highest tertile of the Mediterranean diet score were less likely to develop a cerebrovascular event (0.72; 95% CI 0.54-0.97); no significant association was observed when the analysis was focused only on fatal events (0.76; 95% CI 0.50-1.16), a fact that could be attributed to the small number of deaths occurred.

A randomized, three-arm clinical trial, named PREMID study (13), reported that the pooled effect of Mediterranean diets (combined groups) vs. the control diet was highly protective as regards the secondary end-point which was the development of stroke, after adjusting for sex, age, family history of CVD, smoking status, body-mass index, waist-to-



Table 2. Characteristics of the included systematic reviews and AMSTAR Score

Authors and Year of Publication	Study Design Included	Aims	Alternatives Dietary Patterns	Main Results	Conclusions	AM-STAR Score
Ding and Mozaffarian, 2006 <sup>52</sup>	Large prospective observational studies and randomized clinical trials	To evaluate the optimal dietary habits for stroke prevention	DASH diet, Prudent diet, Vegetarian diet	Mediterranean diet was associated with lower systolic and diastolic BP; reduced serum markers of inflammation, decreased insulin resistance, improved endothelial function, and improved features of the metabolic syndrome; reduced recurrence of coronary heart disease; the prudent pattern was associated with trends toward lower risk of total (RR=0,78; 95% CI 0,61-1,01) and ischemic (RR=0,74; 95% CI 0,54-1,02) stroke	Diets low in sodium and high in potassium lower blood pressure, which will likely reduce stroke risk. Consumption of fruits and vegetables, whole grains, folate, and fatty fish are each likely to reduce stroke risk. A prudent or traditional Mediterranean dietary pattern, which incorporates these individual dietary components as well as intake of legumes and olive oil, may also prevent stroke	5
Faroughi et al, 2013 <sup>53</sup>	Observational studies, cohort studies, clinical trial studies, systematic review, and meta-analysis	To review the studies on the relationship between dietary intake (nutrients, food and beverages), dietary patterns and stroke incidence	DASH diet, Prudent diet, Western diet	Cardioprotective benefits from the adoption of Mediterranean diet; higher consumption of a Mediterranean diet was associated with decreased risk of vascular events	Adherence to Mediterranean diet or DASH diet and increasing the consumption of antioxidant, vitamins, potassium, calcium food sources, vegetables, fruits, and whole grains intake can lower the risk of stroke	5
Grosso et al, 2017 <sup>55</sup>	Prospective studies, Case-control studies, Randomised controlled trials (RCTs)	To review and compare results from prospective investigations and randomized controlled trials (RCTs) exploring the association between Mediterranean diet adherence and CVD incidence and mortality		Highly adherent individuals had lower CVD morbidity and mortality with a decreased risk of about 30% in prospective studies and of about 40–45% in RCTs conducted on patients with high CVD risk.	High adherence to the Mediterranean dietary pattern is associated with lower risk of CVD incidence and mortality, but the effects on specific cardiovascular outcomes between prospective studies and RCTs varies	7
Kontogianni and Panagiotakos et al, 2014 <sup>50</sup>	Observational studies (i.e. prospective cohorts and case-control) and randomized clinical trials (RCT);  Cross-sectional studies were excluded	To systematically present and discuss the up to date available research regarding the relationship between adherence to dietary patterns and stroke.	Prudent diet, DASH diet, “westernize” patterns based on animal foods, sweets and fats.	The Greek EPIC study reported that compared with the lowest tertile, participants in the highest tertile of the Mediterranean diet score were less likely to develop a cerebrovascular event (0,72; 95% CI 0,54-0,97); no significant association was observed when the analysis was focused only on fatal events (0,76, 95% CI 0,50-1,16)  In a meta-analysis by Psaltopoulou et al. it was revealed that high adherence to the Mediterranean dietary pattern was associated with reduced risk for stroke (pooled effect estimate = 0,71, 95% CI 0,57-0,89)  The protective effect concerning stroke was only marginal when moderate vs. low adherence to the traditional Mediterranean diet was examined (0,90, 95% CI 0,81-1,00).  The PREDIMED study, reported that the pooled effect of Mediterranean diets (combined groups) vs. the control diet was highly protective as regards the secondary end-point which was the development of stroke (0,61, 95% CI 0,44- 0,86)	Adherence to dietary patterns such as the Mediterranean or the DASH diet can essentially contribute to stroke prevention, adding a new direction toward stroke prevention on population level	7
Liyanage et al, 2016 <sup>57</sup>	Randomised controlled trials (RCTs)	To define the effects of the Mediterranean diet on cardiovascular events and mortality		The Mediterranean diet may protect against vascular disease, although the quantity and quality of the available evidence is relatively limited and the results must be interpreted with caution	There is a need of another well-conducted, adequately powered trial able to precisely and reliably define the overall balance of benefits and risks associated with the Mediterranean Diet	8

(following table)

Psaltopoulou et al, 2013 <sup>56</sup>	Case-control, cohort and cross-sectional studies	To quantitatively synthesize all studies that examine the association between adherence to a Mediterranean diet and risk of stroke		High adherence to Mediterranean diet was consistently associated with reduced risk for stroke (RR=0,71; 95% CI=0,57–0,89)	Adherence to a Mediterranean diet may contribute to the prevention of stroke	5
Rosato et al, 2017 <sup>54</sup>	Case-control and Cohort studies. Cross-sectional studies and randomized clinical trials were excluded	To provide quantitative evidence of the relationship of MD on incidence/ mortality for CVD, coronary/ischemic heart disease/acute myocardial infarction and stroke ischemic/ hemorrhagic), by sex, geographic region, study design and type of MD score		Favorable role of the MD on CVD, with a decreased risk of about 20–25% for subjects with the highest adherence compared to those with the lowest one. No association was found with hemorrhagic stroke, with no clear explanation. Both ischemic and hemorrhagic stroke have been associated with an unhealthy diet	There is a protective association between MD and the risk CVD, including CHD and ischemic stroke but not hemorrhagic stroke	8
Sherzai et al, 2012 <sup>51</sup>	Observational studies (prospective cohort studies, case-control), randomized controlled trial (RCT)	To present current research regarding the relationship between food groups, dietary patterns, and stroke.	DASH diet, Prudent diet and other dietary patterns	Reduced risk of both CHD and stroke were observed for women in the top quintile of Mediterranean diet adherence as compared to the lowest quintile (RR for stroke, 0,87; 95% CI 0,73–1,02; P for trend, 0,03).	Compliance with a DASH, Mediterranean, or a prudent diet was found to be associated with decreased stroke risk	5
Sofi et al, 2010 <sup>20</sup>	Cohort prospective studies	To update their previous systematic review and meta-analysis of published cohort prospective studies that investigated the effects of adherence to the Mediterranean diet on health status		A 2-point increase of adherence to the Mediterranean diet determined a 8% reduction of death from any causes and a 10% reduction from death and/or incidence of cardio- and cerebrovascular diseases	The estimates of the association of adhering to the Mediterranean diet in terms of protection against overall mortality and incidences of various chronic degenerative diseases were confirmed, with an extension of the findings to some other health outcomes such as stroke and mild cognitive impairment	9

Table 3. Main results of the included meta-analysis and AMSTAR Score

Authors and Year of Publication	Outcome	Pooled Effect Estimate RR (95% CI)	AMSTAR Score
Grosso et al, 2017 <sup>55</sup>	Stroke incidence	0,76 (0,60-0,96)* (Prospective studies)  0,64 ( 0,47-0,86)* (RCTs)	7
Kontogianni and Panagiotakos 2014 <sup>50</sup>	Stroke	0,68 (0,58-0,79)* (high adherence to Mediterranean diet)	7
Liyanage et al, 2016 <sup>57</sup>	Stroke	0,65 ( 0,48-0,88)*	8
Psaltopoulou et al, 2013 <sup>56</sup>	Stroke	0,71 (0,57–0,89)* (high adherence to Mediterranean diet);  0,90 (0,81–1,00) (moderate adherence to Mediterranean diet)	5
Rosato et al, 2017 <sup>54</sup>	Unspecified stroke Ischemic stroke Hemorrhagic stroke	0,73 (0,59-0,91)*  0,82 (0,73-0,92)*  1,01 (0,74-1,37)	8
Sofi et al, 2010 <sup>20</sup>	Overall mortality; Cardiovascular diseases incidence or mortality	0,92 (0,90-0,94)*  0,90 (0,87-0,93)*	9

\*statistically significant

CI: Confidence Interval; RR: Relative Risk

height ratio, hypertension, dyslipidemia and diabetes at baseline. Participants in the PREDIMED study were men aged 55–80 years and women 60–80 years of age with no CVD at enrollment, but they belonged to a high-risk group.

So, for the authors, the adherence to the Mediterranean dietary pattern was associated with reduced risk and mortality rates from stroke. This because, according to them, Mediterranean diet presents strong anti-inflammatory and anti-oxidative effect and the adherence to this diet has been linked to lower systolic and diastolic blood pressure and lower likelihood of hypertension. Moreover, they shared the limitations mentioned in the studies reviewed by them: in some studies there was an inability to evaluate the relationship between sub-types of stroke (hemorrhagic stroke) and dietary factors, due to the limited number of cases; another issue is the difficulty in estimating accurate, long-term nutritional habits of individuals, especially in observational studies, mainly because people often change their habits during lifespan because of various social-financial or medical reasons. They recommended the need for well-designed clinical trials to test compliance to dietary patterns against stroke in high risk individuals.

Also Sherzai *et al.* (51), in their review, complained about the limited number of hemorrhagic stroke cases resulted in inadequate power to perform the necessary analysis.

The study carried out by them included observational studies (i.e. prospective cohorts and case-control studies) and randomized clinical trials (RCT) and they also assessed DASH diet, Prudent diet, and other dietary patterns and food groups. In the review, it mentioned the study of Fung *et al.* (11) who have studied the relationship between a Mediterranean diet and stroke mortality among 74,486 women, aged 38–63 years, from the NHS cohort, followed-up for 20 years; the study recorded 1,763 incident strokes (959 ischemic, 329 hemorrhagic, 475 not clearly identified). Reduced risk of both CHD and stroke were observed for women in the top quintile of Mediterranean diet adherence as compared to the lowest quintile (Relative Risk (RR) for CHD = 0,71; 95% CI, 0,62–0,82; *P* for trend = 0,0001; RR for stroke = 0,87; 95% CI, 0,73–1,02; *P* for trend=0,03).

For all this reasons, Sherzai *et al.* (51), stated that compliance with the Mediterranean diet was associated with decreased stroke risk.

The study carried out by Ding (52) reviewed observational studies and clinical trials to elucidate the optimal dietary habits (including DASH diet, Prudent diet, Vegetarian diet and other nutrients) for stroke prevention.

The authors considered a study by Psaltopoulou *et al.* (64), older than that considered in the Kontogianni and Panagiotakos' review, where adherence to a Mediterranean diet was associated with lower systolic and diastolic BP, in a cross-sectional analysis among 20.343 Greek adults.

Moreover, the review included two randomized clinical trials: the first, among 180 adults with the metabolic syndrome, stated that the Mediterranean diet reduced serum markers of inflammation, decreased insulin resistance, improved endothelial function and improved features of the metabolic syndrome (59); in the second, among 605 post-myocardial infarction patients, a traditional Mediterranean diet reduced recurrence of coronary heart disease (60). In a prospective study, mentioned by them, among 71,768 U.S. women, the

Prudent pattern was associated with trends toward lower risk of total (RR = 0,78, 95% CI 0,61-1,01) and ischemic (RR = 0,74; 95% CI 0,54-1,02) stroke.

They concluded that diets low in sodium and high in potassium lower blood pressure, which will likely reduce stroke risk; consumption of fruits and vegetables, whole grains, folate, and fatty fish are each likely to reduce stroke risk. A prudent or traditional Mediterranean dietary pattern, which incorporates these individual dietary components as well as intake of legumes and olive oil, may also prevent stroke.

The review carried out by Faroughi *et al.* (53) included observational studies, cohort studies, clinical trial studies, systemic review and meta-analysis reviews and assessed single food groups e nutrients and dietary patterns (Mediterranean, Prudent, DASH, Western diet).

About Mediterranean diet, the authors mentioned three studies: a case control study, 500 participants enrolled (250 consecutive patients with a first ischemic stroke and 250 population-based), adherence to the Mediterranean diet assessed by the validated Med Diet Score (theoretical range: 0-55), after various adjustments, each 1/55 unit increase in the Med Diet Score was associated with 17% lower likelihood of having an ischemic stroke (61); the Northern-Manhattan Study as a population-based cohort study, 2568 participants, The Med Diet score was inversely associated with risk of the composite outcome of ischemic stroke, MI, or vascular death (*P*-trend = 0.04) and with vascular death specifically (*P*-trend = 0,02) (2); the third was the meta-analysis by Sofi *et al.* that showed that a two-point increase in adherence to the Mediterranean diet was associated with a significant reduction of overall mortality (RR = 0.92; 95% CI 0,9-0,94) and cardiovascular incidence or mortality (RR = 0,9; 95% CI 0,87-0,93) over 4-20 years of follow-up (20).

In the conclusion, they stated that adherence to Mediterranean diet or DASH diet and increasing the consumption of antioxidant, vitamins, potassium, calcium food sources, vegetables, fruits, and whole grains intake can lower the risk of stroke and they also highlighted the need for more studies to be carried out in this area.

Rosato *et al.* in their study (54), reviewed 26 observational studies (21 cohort studies, 5 case-control study) that quantitatively evaluated the association between adherence to the Mediterranean Diet and CVD. Cross-sectional studies and RCT's were excluded. It was found a consistent inverse relationship across strata of sex, type of MD score (MDS), study design, different type of CVD (CHD/AMI, ischemic stroke), and no association for hemorrhagic stroke. In particular there was a 20-25% reduction of the risk of CVD in subjects with high adherence to the Mediterranean Diet.

According to the authors the protective effect of MD on cardiovascular disease is due to its elevated content of many nutrients that have positive effects of cardiovascular health, such as flavonoid, folate, polyphenols, vitamin C and E, magnesium and potassium. Furthermore, in observational studies, the MD has been shown to be related to a reduction of endothelial dysfunction, carotid atherosclerosis, LDL-cholesterol concentrations and insulin resistance.

The review carried out by Liyanage *et al.* (57) had the aim to explain the effects of Mediterranean diet on cardiovascular outcomes and mortality. Only RCTs that assessing



the effects of Mediterranean diet in adults were included in the analysis.

Although MD had proven to have beneficial effects on cardiovascular diseases, the authors complained the low quantity and quality of available evidence. In fact trials have shown that the Mediterranean diet protects against different types of cardiovascular diseases, but these results are not sufficient to draw definitive recommendations and conclusions.

The authors stated that even if the cohort studies and RCTs conducted to evaluate the relation between Mediterranean diet and cardiovascular outcomes reported a positive association, the observational studies are subjected to confounding and trials are too small and, consequently, susceptible of possible effects of random or systematic errors. Moreover no study reported the risks of adverse effects that the Mediterranean diet could have, so they underlined the need of a well-conducted trial that clarifies the benefits and risks of this diet.

The last review was carried out by Sofi *et al.* (20). The authors have updated their previous systematic review and meta-analysis (17), and they analyzed cohort prospective studies that investigated the association between adherence to the Mediterranean diet and health outcomes, including some other outcomes, such a stroke and mild cognitive impairment, that were not considered in the previous meta-analysis.

They stated that a 2-point increase of adherence to the Mediterranean diet determined a 8% reduction of death from any causes and a 10% reduction from death and/or incidence of cardio- and cerebrovascular diseases. They therefore confirmed the estimates of the association of adhering to the Mediterranean diet in terms of protection against overall mortality and incidences of various chronic degenerative diseases, including stroke.

#### Meta-analysis

The updated meta-analysis by Sofi *et al.* (20) included 7 prospective studies that were not identified and included previously, one of which concerning stroke (14). The meta-analysis conducted after the inclusion of these recent studies showed that a 2-point increase in adherence to the Mediterranean diet was associated with a significant reduction of overall mortality (RR = 0,92; 95% CI 0,90-0,94) and cardiovascular incidence or mortality (RR = 0,90; 95% CI 0,87-0,93) (Table 3). The meta-regression analysis conducted by grouping studies according to some characteristics, such as the number of subjects studied, number of cases observed, country of origin of the patients, age of the patients, and length of follow-up, showed that sample size was the most significant contributor to the model because it significantly influenced the estimate of the association for overall mortality ( $\beta = 0,059 \pm 0,018$ ;  $P = 0,013$ ).

The Kontogianni and Panagiotakos' meta-analysis (50) included the meta-analysis carried out by Psaltopoulou *et al.* and three additional studies (13,58,62). It was revealed that greater adherence to the Mediterranean diet was associated with 32% lower risk of stroke events (pooled effect estimate = 0,68; 95% CI 0,58-0,79) (Table 3). These findings based on a total sample of 195,875 participants enhanced the

previously reported meta-analysis underlying a consistent, protective effect of Mediterranean diet on stroke incidence. When the additional three studies were combined separately the pooled effect estimate was lower as compared with the pooled effect reported in the meta-analysis by Psaltopoulou *et al.* (56) (i.e., pooled effect estimate = 0,65; 95% CI 0,53-0,80 vs. 0,71; 95% CI 0,57-0,89).

The meta-analysis by Rosato *et al.* (54) reported a pooled RR for unspecified stroke, based on 6 studies, of 0,73 (95% CI 0,59-0,91) for the highest versus the lowest category of the MDS. The inverse relationship of MD on stroke was significant across strata of study design (RR 0,77 for cohort studies and 0,12 for the single case-control study), sex (RR 0,83 for women and 0,70 for men), and geographic area (RR 0,76 for Mediterranean and 0,66 for non-Mediterranean countries), and the MDS used (RR = 0,74; 95% CI 0,62-0,89, for TS, and 0,36; 95% CI 0,05-2,41, for the two studies using alternative scores). The pooled RR for the association between MD with ischemic and hemorrhagic stroke, considered in five and four studies, was 0,82 (95% CI 0,73-0,92) for ischemic and 1,01 (95% CI 0,74-1,37) for hemorrhagic stroke.

Grosso *et al.* (55) conducted a meta-analysis that assessed the association between the high adherence to the Mediterranean diet and CVD incidence and mortality; in this meta-analysis were included 20 prospective studies and 4 RCTs. CVD events taken into account concerned myocardial infarction (MI), coronary heart disease (CHD) and stroke. 13 prospective studies were pooled together to evaluate the risk of CVD incidence and mortality in relation with MD adherence. High adherence to the diet has been shown to decrease risk of CVD incidence (RR= 0,73; 95% CI 0,66-0,80) and mortality (RR 0,75; 95% CI 0,68-0,83), compared to a low adherence. Regarding stroke incidence, 5 studies were analyzed and it resulted a risk reduction with a high adherence to the MD (RR = 0,76; 95% CI 0,60-0,96). Even the four RCTs included in the meta-analysis (conducted on patients with high CVD risk) have proven a 40% decrease incidence of CVD (for stroke, RR = 0,64; 95% CI 0,47-0,86) and mortality (RR = 0,59; 95% CI 0,38-0,93). According to the authors the protective effects of the MD seem to be due to specific foods such as legumes, vegetable, fruit and olive oil and should be analyzed in future RCTs to better understand their effectiveness.

The meta-analysis carried out by Psaltopoulou *et al.* (56) had the aim to quantitatively synthesize all studies that examine the association between adherence to a Mediterranean diet and risk of stroke, depression, cognitive impairment, and Parkinson disease.

The authors included twenty-two studies, 11 of them pertained to stroke (9 cohorts, 2 case-control studies). Statistical analyses included pooling of studies at 2 separate levels (high vs low adherence; moderate vs low adherence). High adherence to Mediterranean diet was consistently associated with reduced risk for stroke (pooled effect estimate = 0,71; 95% CI 0,57-0,89); conversely to the association on high adherence, the protective trend in moderate adherence to Mediterranean diet was only marginal (pooled effect estimate = 0,90; 95% CI 0,81-1,00) (Table 3). In meta-regression analyses the protective effects mediated by high adherence to Mediterranean diet in terms of risk for stroke

seemed more pronounced among males (exponentiated coefficient=0,84; 95% CI 0,74–0,94), the potentially protective effects mediated by moderate adherence in terms of stroke risk (exponentiated coefficient = 0,94; 95% CI 0,88–0,99) seemed to follow the same pattern. So they stated that high adherence to the Mediterranean diet, seems beneficial along many central nervous system related axes, as it was inversely associated with stroke, cognitive impairment, and depression, whereas its protective effects regarding stroke remained only marginal in moderate adherence. In conclusion they recommended future studies that should ideally encompass a longitudinal cohort design with sufficiently long follow-up periods and meticulous ascertainment of exposure and outcomes.

In the meta-analysis carried out by Liyanage *et al.* (57) among the trials included, three concerned coronary events and stroke, with 167 cerebrovascular events. The adherence to the Mediterranean diet was associated with a relative risk of 0,65 (95% CI 0,48–0,88) for stroke.

## Discussion

### *Main finding of this study*

This is the first overview in scientific literature carried out to assess the association between Mediterranean diet pattern and stroke.

The reviews included in this study analyzed the association between dietary patterns, food groups, nutrients and stroke, and their possible preventive role. All the authors agreed in stating that the Mediterranean diet reduced the risk and mortality rates from stroke or CVD. They considered several studies, observational studies and randomized clinical trials, that evaluated the effects of the Mediterranean diet on health outcomes, among which the PREDIMED Study (13), the Lyon Diet Heart Study (60,68) and the Northern Manhattan Study (63) and. Moreover, six meta-analysis were carried out which highlighted that high adherence to the Mediterranean diet was associated with decreased stroke risk, overall mortality and cardiovascular diseases incidence or mortality (20,50,54–57).

This dietary pattern has been associated with lower concentrations of inflammatory markers (50) and endothelial dysfunction in healthy individuals, high-risk patients, and those with a history of coronary events (38,34). In addition, adherence to this dietary pattern has been linked to weight loss, lower blood pressure, a more favorable ratio of total to HDL cholesterol, lower oxidized LDL concentrations, lower glucose levels and lower carotid intima-media thickness in patients with high atherosclerotic burden (39,40,50). This because the Mediterranean diet is rich of foods with a beneficial effect on cardiovascular health such as fruits, vegetables, legumes, nuts, whole grains, low-fat dairy products, cereal fiber and fish (36,38,52). The bulk of the evidence presented in the selected reviews was obtained from prospective cohort and case-control studies in which the role of residual confounding cannot be ignored. Case-control studies are mostly inappropriate to study the temporal sequence and usually suffer from a “survival bias” due to an inability to study fatal outcomes.

They do, however, offer an early opportunity to examine associations and identify potential avenues for intervention related research. Observational cohort studies are able to evaluate long-term effects of dietary exposures and often provide a wide range of exposure, but are subject to unknown confounders which cannot be adjusted for measurement errors in dietary ascertainment. Effects of changes in dietary exposures occurring during the long period of observation are also difficult to evaluate. The dose of exposure is a critical variable in an area like diet, where many of the nutrients are physiological requirements at a certain level but may pose risk of cardiovascular dysfunction and disease at other levels. Ascertainment of dose-related effects is essential, whether the exposure is salt, alcohol or fish. The authors complained about the small number of trials specifically designed to test the effect on diet on stroke as the primary outcome and the inability to evaluate, in some studies, the relationship between sub-types of stroke (hemorrhagic) and dietary factors, mainly due to the limited number of cases.

They recommended the need for well-designed clinical trials to test compliance to dietary patterns against stroke in high risk individuals, since clinical trials, if well designed, provide the best framework for studying associations, as free from the effects of bias and confounding as possible, considering that people often change their habits during lifespan because of various social-financial or medical reasons and it is difficult to estimate accurately long-term nutrition habits of individuals in observational studies.

### *What is already known on this topic*

Worldwide, stroke is the most common cardiovascular disorder after heart disease. Of the 17.5 million deaths due to cardiovascular disease in 2012, an estimated 7.4 million were due to heart attacks (heart disease) and 6.7 million were due to strokes (66). According to WHO, heart disease and stroke were among the top three causes of years of life lost due to premature mortality globally (67). For many, surviving a stroke is a fate worse than death; stroke is the second leading cause of disability, after dementia (68). Disability may include loss of vision and/or speech, paralysis and confusion. For all these reasons, prevention takes central importance, and nutrition has proven to be an effective means to prevent stroke (69).

There is no reason to follow other diets than the Mediterranean one. However Southern European Countries are rapidly withdrawing from this food model, preferring products of the Western diet pattern, rich in refined grains, animal fats, sugars, processed meat, but poor in legumes, cereals, fruits and vegetables. Furthermore, as a result of industrialization, urbanization, economic development and food market globalization, there has been a significant change in dietary habits and physical activity levels worldwide (70).

The reason people keep on shifting from healthy to unhealthy dietary habits remains open to several interpretations. A wide range of factors can affect food consumption such as food availability, food accessibility, and food choices, which in turn may be influenced by geography, demography, disposable income, socio-economic status, urbanization, globalization, religion, culture, marketing, and consumer

attitude (71,72,73,74). Social changes seem to have consistently contributed to radical reversal in dietary habits in Mediterranean societies even though developing countries are oriented towards westernized diets as well. Increasing prices of some of the major food items of Mediterranean diet seem to have brought people to abandon this eating pattern in favor of less expensive products which allow to save money but are definitively unhealthy.

The new diets tend to be energy-dense, supplying more energy, but fewer nutrients per gram (75). Refined grains, added sugars, and added fats have become the staple foods of industrialized nations (76). Developing nations undergoing nutrition transition also replace the traditional plant-based diets with more simple sugars and more added fats (77). Such energy-dense foods, high in fats, sugars and sodium, have the advantage of being good-tasting, affordable, and convenient. Providing dietary energy at very low cost, they are preferentially consumed by lower income groups.

There is a need to change the direction and dimensions of the global CVD epidemic through local, national and global levels policy interventions, which promote the availability, affordability and acceptability of health diets and reduce the marketing and consumption of unhealthy foods.

Prevention policies should consider the economic barriers associated with following a healthy diet, because cost may be a prohibitive factor. Lowering the prices of some basic products such as fruits and vegetables and improving their availability in the most citizens-attended places should represent the first step to reclaim a healthy living model. Governments must work with the food industry to influence production, processing, pricing and labelling of food products so that these goals can be met. Consumer education must be enhanced so that informed choices can be made, even as the availability of healthier foods is promoted through such measures. These constructive policy and initiatives to promote and protect global cardiovascular health through diet and nutrition need to be included onto the national and global health agenda through multi-institutional collaboration and increased through inter-sectoral coordination.

### Limitations of this study

The possible limitation of this overview could be due to the possible incomplete retrieval of identified research and to the reporting bias. However the evidences from the analyzed studies show that a high adherence to the Mediterranean diet is inversely associated with stroke risk, and can modify the costs of its management.

### Conclusions

The rising incidence of stroke continues to strain our health care system, requiring and pushing towards the development of new preventive strategies. Dietary recommendations for stroke risk reduction should focus on increased consumption of Mediterranean diet and the prevention policies should implement adherence to this healthy diet, breaking down economic barriers and reducing costs, and

increase the consumers' and policy makers' general knowledge of the concept of healthy eating, leading to better decisions in the marketplace, and thus improved population health status.

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