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Review Article

Dietary patterns and stroke: A systematic review and re-meta-analysis

Meropi D. Kontogianni, Demosthenes B. Panagiotakos *

Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University, Athens, Greece

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ABSTRACT

The effect of diet on the development of stroke has recently achieved much interest by various research groups, but with inconclusive results. The aim of the present review was to systematically present and discuss the up to date available research regarding the relationship between adherence to dietary patterns and stroke. Studies included were observational and randomized clinical trials. Internet searches until May 31, 2014, retrieved 152 potentially relevant papers; of them, 34 were excluded on the basis that did not report data on humans, 3 were in language other than English, 2 were excluded because they had a cross-sectional design, 3 because they reported data on secondary prevention and 82 were excluded on the basis of irrelevant research. One article was a recent meta-analysis on Mediterranean diet, stroke, cognitive impairment and depression and was used as a basis for a re-meta-analysis with the additional papers published after the publication of the later meta-analysis. The existing evidence suggests that adherence to healthy dietary patterns (i.e., Mediterranean or DASH or plant based "prudent") was associated with reduced risk for stroke, whereas limited data exist supporting a detrimental effect of westernized dietary patterns. Moreover, the applied re-meta-analysis, based on a total sample of 195,875 participants enhanced the previously reported meta-analysis underlying a consistent, protective effect of higher adherence to the Mediterranean diet on stroke incidence (pooled relative risk 0.68, 95% CI 0.58, 0.79). Thus, a healthy dietary pattern exerts a beneficial effect on stroke incidence and mortality, adding a new direction toward stroke prevention on population level.

Contents

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; EPIC, European Prospective Investigation into Cancer and Nutrition; HDL, high density lipoprotein; HR, hazard ratio; LDL, low density lipoprotein; MOOSE, Meta-analysis of Observational Studies in Epidemiology guidelines; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR, relative risk.

* Corresponding author at: 46 Paleon Polemiston St., Glyfada, Attica, 166 74, Greece. Tel.: +30 210 9603116; fax: +30 210 9600719.
E-mail address: d.b.panagiotakos@usa.net (D.B. Panagiotakos).

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1. Introduction

Cardiovascular disease (CVD), including coronary heart disease and stroke, remain the leading cause of death and disability in developed world, affecting almost half of the population at some time point during lifespan. According to the World Health Organization [1], 13.5 million people died from CVD in 2008, representing 30% of all global deaths. Of these deaths, 6.2 million were due to stroke. It has also been estimated, through predictive risk models, that the number of people who die due to CVD will reach to 23.3 million by 2030; and, the stroke death rates will continue to rise. In addition, development of non-fatal stroke events has also shown an increase the last decades, whereas it has been suggested that up to 80% of stroke events could have been prevented [2]. The later deserves special attention, especially after taking into account that stroke affects physical, cognitive and emotional functioning, leads individuals even to severe disability, and causes various social and economical changes [2,3].

It is now widely adopted that CVD can be largely prevented by addressing modifiable risk factors, such as tobacco use, unhealthy diet and obesity, physical inactivity, high blood pressure, diabetes and raised lipids [4,5]. Extensive research has been done over the past decades in order to advance understanding of stroke pathophysiology and treatment, including epidemiological research for stroke prevention. Epidemiological studies have extensively focused on dietary habits and their impact on risk for stroke, as one of the modifiable CVD risk factors. Moreover, the American Heart and the American Stroke Association strongly promote a healthy way of living, including consuming healthy dietary patterns and exercising on a regular basis, achieving ideal body weight, and abstinence from smoking, in order to prevent a stroke episode [2].

As regards diet, much of the health-related research to date has focused on individual nutrients or foods and food groups and their effect on stroke, whereas broader research is now investigating the impact of diet as a whole. People consume meals consisting of several food items containing a broad combination of nutrients. Therefore, complicated or cumulative inter-correlations and interactions between nutrients and food groups should be studied. Rather than assessing single nutrients, foods, or food groups, it has been suggested that a holistic dietary approach, which examines the effect of dietary patterns in terms of chronic disease prevention and treatment, may be a more valuable approach to evaluating associations between diet and biological markers and/or disease outcomes [6]. Currently, there are two approaches that have been suggested in order to determine adherence to dietary patterns. One approach is based on the composition of predefined diet quality indices using current nutrition knowledge (e.g. the MedDietScore, the DASH diet score). This method is known as “theoretically defined dietary patterns”. The other approach is based on statistical techniques, such as principal component analysis, factor analysis and cluster analysis and it is known as “empirically or data-driven defined dietary patterns” [7].

The past few years several observational studies and a meta-analysis have supported that adherence to a healthy dietary pattern may protect the development of a fatal or non-fatal stroke event. However, the heterogeneity in the studied populations, the dietary patterns assessed, as well as the fact that other studies did not confirm the previous findings lead the scientific community to confusion. Therefore, the aim of the present review was to systematically present and discuss the up to date available research regarding the relationship between adherence to dietary patterns (both theoretically and empirically defined) and stroke.

2. Methods

2.1. Data sources and searches

The current review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8].

Internet searches in PubMed, Embase and Scopus databases up to May 31, 2014, using a search strategy that included the following keywords: “Stroke”, “Mediterranean diet”, “DASH diet”, “Dietary pattern(s)”, “Food Habits”, “Diet”, and other relevant keywords to identify original research studies related to the aim of the paper, were performed. References from the extracted articles and reviews were also used, to complete the data bank. The relevance of studies was performed using a hierarchical approach based on title, abstract, and the full manuscript. In case the full article was not accessible, it was requested from the corresponding author.

2.2. Study’s selection criteria

Studies included were observational (i.e. prospective cohorts and case–control) 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. Moreover, exclusion criteria included articles that: were focused on single foods or nutrients, reported results not fully obtainable from the authors, and finally papers not published in English language. The authors collected the relevant papers, whereas two other authors independently reviewed the literature (CK, EK); disagreements were solved by consensus and by the opinion of a fifth evaluator (CMK), when necessary.

2.3. Data extraction and quality assessment

The following characteristics were extracted from the original papers, using a standardized data extraction form: design of the study (case–control or prospective cohort or intervention), lead author (for citation purposes), year of publication, country of origin, sample size, follow-up duration, effect size measurements (i.e., hazard ratio/relative risk, odds ratio, *b*-coefficients and their corresponding 95% confidence intervals) and variables that entered into the model as potential confounding factors. The quality of the studies was evaluated according to the adjustment for potential mediators (e.g., demographic, anthropometric and traditional risk factors).

2.4. Data synthesis and analysis

The primary Internet search resulted in 152 papers that were scanned to ensure they were consistent to the search criteria. Of

them, 34 were excluded on the basis that did not report data on humans, 3 were in language other than English and 82 were excluded on the basis of the title or abstract (i.e., irrelevant research hypothesis studied). Of the remaining 33 articles, 2 were excluded because they had a cross sectional design and 3 because they reported data on secondary prevention. One article was a recent meta-analysis on Mediterranean diet, stroke, cognitive impairment and depression [9]. The present re-meta-analysis included the aforementioned meta-analysis and three additional studies [10–12] and data analysis was performed in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [13]. Analysis included pooling of studies at one exposure level (high vs. low adherence to the Mediterranean diet). Random-effects (Der Simonian-Laird) models were used to calculate the pooled effect estimates. Between-study heterogeneity was assessed through Cochran *Q* statistic and by estimating I^2. Higher values of I^2 (>50%) and significant Cochran *Q* suggests heterogeneity between the previous meta-analysis by Psaltopoulou et al., and the additional studies included in the present work. No meta-regression analysis, or sub-group analyses were performed due to the small number of additional studies; moreover, publication bias was not assessed because of the same reason.

2.5. Statistical software

Statistical calculations were performed using STATA software version 12.0 (College Station, TX, USA); meta-analysis was performed using the *metan* command.

3. Results

3.1. a-posterior defined dietary patterns and stroke

Prospective studies exploring the associations between adherence to a-posterior dietary patterns and the risk for or mortality from stoke are presented in Table 1. Studies come from different countries including data from American, European and Asian regions and dietary patterns were derived through factor analysis [10,14–20]. The majority of the studies revealed a "prudent" or "healthy" dietary pattern based mainly on plant foods, as well as "westernized" patterns, based on animal foods, sweets and fats. Most of the studies found either a protective effect of plant based patterns against stroke [14,15,17,20] or a detrimental effect of the adherence to westernized patterns [15,19]. However results are difficult to combine and be conclusive.

In addition, Kastorini et al. [21] in a Greek case–control study of 250 consecutive patients with a first stroke and 250 age and sex matched controls derived dietary patterns from principal component analysis, based on food frequency questionnaire (FFQ) data. Five dietary patterns were revealed, while in multivariate analysis models *Component 1* (heavily loaded with pasta, rice, potatoes and eggs) was associated with higher likelihood for stroke (odds ratio (OR) 1.42, 95% CI 1.03, 1.94) and *Component 2* (heavily loaded with fish, legumes, salads and fruits) was associated with lower likelihood for stroke (OR: 0.69, 95% CI 0.49, 0.96).

3.2. a priori defined dietary patterns and stroke

3.2.1. Mediterranean diet

The term "Mediterranean diet" has been widely used in order to describe the traditional dietary habits of people in Crete, South Italy and other Mediterranean countries during the 1960s. It is schematically depicted as a food pyramid. This dietary pattern is characterized by plentiful plant foods (fruits, vegetables, breads, other forms of cereals, beans, nuts, and seeds), olive oil as the principal source of fat, moderate amounts of dairy products (mainly cheese and yogurt), low to moderate amounts of fish and poultry, red meat in low amounts and wine consumed in low to moderate quantities, usually with meals [22]. There are several beneficial nutrients that are abundant in the Mediterranean diet, such as monounsaturated fatty acids, a balanced ratio of omega-6/omega-3 essential fatty acids, high amounts of fiber, antioxidants such as vitamins E and C, resveratrol, polyphenols, selenium, glutathione, and many others that are still under investigation.

In a very recent meta-analysis by Psaltopoulou et al. [9] 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), as well as depression (0.68, 95% CI 0.54, 0.86) and cognitive impairment (0.60, 95% CI 0.43, 0.83); conditions that have been consistently associated with stroke. Moreover, as reported by the authors, the protective effect of the Mediterranean diet on stroke was reproducible among case-control and longitudinal cohort studies, as well. However, it should be noted that 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). At the same time of the aforementioned meta-analysis the Greek-EPIC (European Prospective Investigation into Cancer and Nutrition) cohort reported their findings of Mediterranean diet on cerebrovascular diseases [12]. The data used in the analysis were collected in the context of the Greek component of the (EPIC) and included 23,601 participants that were followed-up for a median period of 10.6 years. The authors 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), a fact that could be attributed to the small number of deaths occurred [12]. Following the publication of the aforementioned meta-analysis, the PREDIMED study (Mediterranean diet in the primary prevention of cardiovascular diseases), a randomized, three-arm clinical trial (i.e., Mediterranean diet with nuts or extra virgin olive oil, and control diet) 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), after adjusting for sex, age, family history of CVD, smoking status, body-mass index, waist-to-height ratio, hypertension, dyslipidemia and diabetes at baseline [11]. At this point it should be noted that participants in the PREDIMED study were men aged 55–80 years and women 60–80 years of age with no CVD at enrollment, but who had either type 2 diabetes mellitus or at least three of the following major CVD risk factors: smoking, hypertension, elevated low-density lipoprotein, elevated cholesterol levels, obesity or family history of CVD; in other words, they belonged to a high-risk group. More recently, Chan et al. [10] examined whether stroke risk was associated with dietary patterns identified by both a priori and a-posterior approaches, using data from 1338 Chinese men and 1397 Chinese women aged 65 years or more, participating in a cohort study examining the risk factors for osteoporosis in Hong Kong. The authors reported that adherence to the Mediterranean dietary pattern (highest vs. lowest tertile of the diet score used) was inversely associated with risk of stroke (0.55, 95% CI 0.31, 0.99) in men, but not in women.

Based on the meta-analysis reported above and the three additional studies retrieved during the present systematic review, a re-meta-analysis was performed. It was revealed that greater adherence to the Mediterranean diet was associated with 32% lower risk of stroke events (0.68, 95% CI 0.58, 0.79, Figure 1). Cohran's *Q* was not significant ($Q = 1.23$, $p = 0.74$) and I^2 was 0.0%; both suggesting lack of heterogeneity. These findings based on a total sample of 195,875 participants enhanced the previously reported

Table 1
Studies exploring the effect of adherence to "a-posterior" dietary patterns on the risk for and mortality from stroke.

Reference	Study sample and design	Patterns	Findings
Fung et al. [15]	Nurses' Health Study. Prospective evaluation of 71,768 women who were free of CVD, diabetes or cancer. Dietary patterns were derived by factor analysis based on validated FFQ administered every 2–4 years. Follow up from 1984 to 1998.	*Prudent*: High consumption of vegetables, fruit, legumes, fish, and whole grains. *Western*: High consumption of red and processed meats, refined grains, sweets and desserts.	RR of 1.58 (95% CI 1.15, 2.15; $p < 0.001$ for trend) for total strokes and 1.56 (95% CI 1.05, 2.33; $p = 0.02$ for trend) for ischemic strokes, after adjusting for potential confounders, when comparing the highest with lowest quintiles of the *Western* pattern. For the *Prudent* pattern, the RRs comparing extreme quintiles were 0.78 (95% CI 0.61, 1.01) for total stroke and 0.74 (95% CI 0.54, 1.02) for ischemic stroke.
Judd et al. [19]	Reasons for geographic and racial differences in stroke (REGARDS) study. Sample of 30,239 black and white Americans. Dietary patterns were derived using factor analysis and foods from FFQ. Median of follow-up was 5.7 years.	*Convenience*: High in Chinese, Mexican, meat and pasta dishes and pizza. *Plant-based*: High in fruits, vegetables, cereals and beans. *Sweets/fats*: High in sweets and added fats. *Southern*: High in organ and processed meats, fried foods, eggs, butter and sugar-sweetened beverages. *Alcohol/salads*: High in vegetable, salad dressings and alcoholic drinks.	The *Southern* pattern was associated with a 39% increased risk of stroke (highest vs. lowest quartile HR: 1.39; 95% CI 1.05, 1.84, $p = 0.009$ for trend). This association was attenuated with the addition of covariates, but the direction of the association remained significant ($p = 0.05$). The *Sweets/fats* pattern was associated with lower risk for stroke (highest vs. lowest quartile HR: 0.80; 95% CI 0.61, 1.04) in multivariate analysis. The *Plant-based* pattern was also associated with lower risk for stroke but lost significance in multivariate analysis. Neither the *Convenience* pattern nor the *Alcohol/salads* pattern was associated with risk of stroke. Including *Southern* pattern in the model mediated the black–white risk of stroke by 63%.
Stricker et al. [20]	EPIC-NL study. Sample of 35,910 free of CVD at baseline. Baseline dietary intake was measured using a validated FFQ. Dietary patterns derived from principal component (PCA) and k-means cluster analysis (KCA). Follow up of 13 years.	Both analyses extracted: *Prudent*: High consumption of fish, high-fiber products, raw vegetables and wine. *Western*: High consumption of French fries, fast food, low-fiber products, other alcoholic drinks and soft drinks with sugar.	The *Prudent* component was associated with a reduced risk of stroke (HR for extreme quartiles: 0.68, 95% CI 0.53, 0.88). The *Western* pattern was not related to the risk for stroke. The *Prudent* cluster was associated with a decreased risk of stroke (HR: 0.79, 95% CI 0.67, 0.94) compared to the western cluster in multivariate analysis. The *Prudent* component was associated with a reduced risk of ischemic stroke (highest vs. lowest quartile: 0.67, 95% CI 0.48, 0.95, $p = 0.023$ for trend) after adjustment for potential confounders. None of the patterns was statistically significantly related to hemorrhagic stroke (probably due to low number of cases).
Shimazu et al. [17]	Prospective assessment of 40,547 Japanese men and women without a history of diabetes, CVD or cancer at the baseline in 1994. Patterns were derived through principal component analysis based on a validated FFQ. Follow up of 7 years.	*Japanese*: Highly correlated with soybean products, fish, seaweeds, vegetables, fruits and green tea. *Animal food*: Loaded heavily on various animal-derived foods, coffee and alcoholic beverages. *DFA*: Loaded heavily on dairy products, margarine, fruits and vegetables, and negatively loaded on rice, miso soup and alcoholic beverages.	The multivariate HR of total stroke mortality across increasing quartiles of the *Japanese* pattern score was (highest vs. lowest quartile): 0.64, 95% CI 0.47, 0.85, $p = 0.003$ for trend, of cerebral infraction (highest vs. lowest quartile: 0.60, 95% CI 0.37, 0.99, $p = 0.03$ for trend) and of intracerebral hemorrhage (highest vs. lowest quartile: 0.60, 95% CI 0.35, 1.01, $p = 0.04$ for trend). The *Animal food and the DFA* pattern were not associated with the risk of stroke.
Maruyama et al. [16]	Japan Collaborative Cohort (JACC) Study. Analysis included 64,037 Japanese men and women free of CVD. Dietary patterns were derived through factor analysis based on FFQ data. Median follow up was 12.6 years.	*Vegetable*: Dominated by fresh fish, vegetables, fungi, potatoes, algae, tofu and fruits. *Animal food*: Dominated by meats, fishes and deep-fried foods or tempura. *Dairy product*: Milk and dairy products, butter, margarine, fruits, coffee and tea.	The *Animal food* and the *Vegetable* patterns were not associated with mortality from stroke in both sexes. The HRs of mortality from stroke across the increasing quintiles of the *Dairy product* pattern were (highest vs. lowest quintile): 0.65, 95% CI 0.49, 0.86, p for trend = 0.01 for men and 0.70, 95% CI 0.51, 0.97, p for trend = 0.02 for women.
Cai et al. [14]	The Shanghai Women's Health Study is a population based cohort of 74,942 women age 40–70 years at baseline. Dietary patterns were derived through principal component analysis, based on FFQ data. The average follow-up was 5.7 years.	*Vegetable rich*: Heavily loaded with vegetables such as green beans and yard long beans. *Fruit rich*: Mainly loaded with fruits. *Meat-rich*: Loaded with meat, poultry, and animal organs.	The multivariate HR of stroke mortality across increasing quartiles of the *Fruit rich* pattern was (highest vs. lowest quartile): 0.53, 95% CI 0.34, 0.82, p for trend <0.001. The other two patterns were not associated with stroke mortality.
Chan et al. [10]	Cohort of 1338 Chinese men and 1397 Chinese women from Hong Kong. Dietary patterns were derived through factor analysis, based on FFQ data. Median follow up was 5.7 years.	*Vegetables-fruits*: Frequent intake of vegetables, fruits, soy and soy products, and legumes. *Snacks-drinks-milk products*: Frequent intake of condiments, drinks, fast food, French fries, potato chips, bakery products, nuts, milk products, and egg. *Meat-fish*: Frequent intake of dim sum, red and processed meats, poultry, fish and seafood.	None of the derived patterns were associated with risk of incident stroke in either men or women.

RR: relative risk; CI: confidence interval; HR: hazard ratio; OR: odds ratio; FFQ: food frequency questionnaire; CVD: cardiovascular disease.

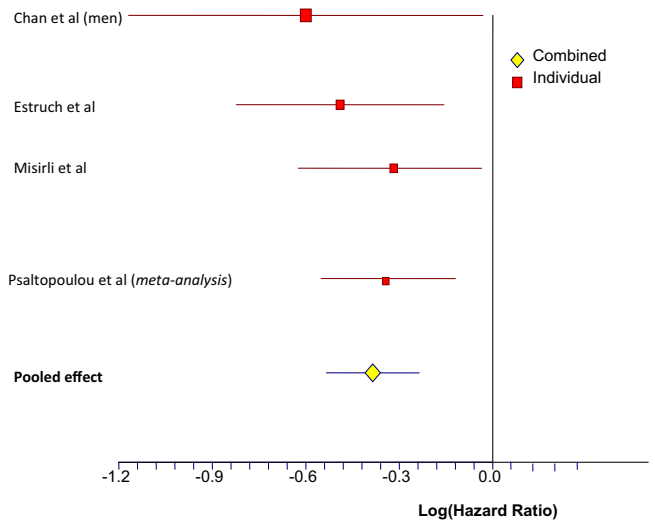

Fig. 1. Forest plot of studies that evaluated the effect of higher adherence to the Mediterranean diet on the development of stroke [squares represent individual study's effect size, i.e., relative risk or hazard ratios or odds ratios and diamond represents the combined effect size; extended lines show 95% confidence intervals (CI) of the effect size].

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. (i.e., 0.65, 95% CI 0.53, 0.80 vs. 0.71, 95% CI 0.57, 0.89).

3.2.2. *DASH diet and stroke*

The Dietary Approaches to Stop Hypertension (DASH) diet is a pattern that was tested, in the most well known controlled feeding study, against hypertension [23]. The composition of the DASH diet is 27% calories from total fat, 6% calories from SFA, 18% calories from protein, 55% calories from carbohydrate, 150 mg cholesterol and usually two levels of sodium intake, 2400 mg or 1500 mg. The calcium, magnesium and fiber content of the diet is also higher than the typical American diet, with 1250 mg calcium, 4700 mg potassium and 30 grams fiber. The DASH diet was demonstrated to be effective as first-line therapy in individuals with stage I isolated systolic hypertension (i.e., with a systolic blood pressure of 140–159 mmHg and a diastolic blood pressure below 90 mmHg), with 78% of the persons on the DASH diet reducing their systolic blood pressure to <140 mmHg, in comparison to 24% in the control group [24]. DASH has also proven to be effective in lowering plasma levels of total and LDL-C but these changes were also accompanied by a reduction in HDL-C levels. The results of that study clearly showed that a diet high in fruits, vegetables and low-fat dairy products, but low in saturated and total fat, reduces blood pressure in hypertensive and normotensive individuals (more so than the control diet). Associations between adherence to the DASH dietary pattern and several CVD outcomes have been also explored.

In 2013 Salehi-Abargouei et al. [25] published a meta-analysis on observational prospective studies summarizing the longitudinal effects of a DASH-style diet on the incidence of CVDs, including stroke. Meta-analysis in 150,191 adults, participated in the studies included, showed that high adherence to a DASH-style diet significantly decreased the risk for stroke (0.81; 95% CI 0.72, 0.92), and heterogeneity between studies was not found (Q test, $p = 0.912$; $I^2 = 0.0\%$). Furthermore, linear regression comparing higher ntiles with the lowest (reference p-ntile) as a dependent variable and p-ntile numbers as a covariate revealed a significant negative trend between adherence to a DASH-style diet score and the risk for stroke ($\beta = -0.005$; $p = 0.001$).

In the same year a prospective study from Taiwan including 1420 participants through a follow up of up to 12 years, explored the effect of the adherence to a DASH dietary pattern (as this was assessed through two scores based on FFQ data) on the risk for ischemic stroke [26]. Although the DASH-food score was not significantly associated with the risk for overall stroke, the DASH nutrient score, combining adherence scores for the five key nutrients targeted in the DASH dietary pattern, namely saturated fat, dietary fiber, calcium, potassium, and magnesium, was significantly associated with the risk for overall and ischemic stroke in an inverse relationship. In specific, the hazard ratio (HR) of overall stroke comparing with highest to the lowest tertile was 0.63 (95% CI 0.41, 0.98) and of ischemic stroke 0.54 (95% CI 0.33, 0.88). Additionally, in the Chinese cohort reported above [10] a borderline inverse association was observed between DASH dietary pattern (score ≥4 vs. <4) and stroke risk in men (HR of the DASH score of ≥4.5 = 0.62, 95% CI 0.38, 1.04), but not in women.

The association between a DASH-like diet with stroke mortality was also explored in the prospective cohort of Parikh et al. [27] in a sample of 5532 hypertensive adults in the Third National Health and Nutrition Examination Survey. Adherence to a DASH-like diet was based on dietary data from 24 h recalls. Of the 5532 participants with hypertension, 391 (7.1%) consumed a DASH-like diet and 5141 (92.9%) consumed a typical American diet. Average follow-up time was 8.2 person-years. The DASH-like group had lower unadjusted mortality rates per 1000 person-years of follow-up for stroke mortality ($p < 0.001$), whereas in multivariate models the DASH-like diet was associated with lower mortality from stroke (HR 0.11, 95% CI 0.03, 0.47).

4. Discussion and conclusive remarks

The present review tried to shed light on the associations between long-term adherence to dietary patterns and the risk for or mortality from stroke. The existing evidence indicates that adherence to the Mediterranean dietary pattern or the DASH dietary pattern is associated with reduced risk and mortality rates from stroke. Furthermore, adherence to plant based "prudent" or "healthy" dietary patterns have been also associated with reduced risk and mortality from stroke, whereas limited data exist supporting a detrimental effect of westernized dietary patterns on stroke risk. However, the present systematic review and re-analysis of a previously published meta-analysis with the addition of new studies, shares the limitations mentioned in the studies reviewed. Particularly, in some studies there was an inability to evaluate the relationship between sub-types of stroke and dietary factors. In some cases the statistical power of the studies was inadequate to perform sub-group analyses according to stroke type, mainly due to the limited number of hemorrhagic stroke 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.

Stroke is classically characterized as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, intra-cerebral hemorrhage, and subarachnoid hemorrhage, and is a major cause of disability and death worldwide [28]. The most common mechanism of hemorrhagic stroke is hypertensive small vessel disease, while athero-thrombotic stroke can develop as a consequence of thrombosis in situ, or following embolic occlusion of a cerebral blood vessel, the latter usually arising from the heart or atherosclerotic plaques in the carotid artery and aortic arch, or by hypo-perfusion. Persistent sub-clinical systematic inflammation

and oxidative stress leading to endothelial dysfunction, result in atherosclerosis and atherothrombotic obstructions in various locations [29].

Healthy dietary patterns have been proven to prevent both sub-clinical inflammation and oxidative stress. Mediterranean diet presents strong anti-inflammatory and anti-oxidative effects. Adherence to the MD has been consistently associated with decreased biomarkers of subclinical inflammation [30–32] and has been proposed to protect individuals from oxidative stress [33,34], defined as the persistent imbalance between free radical formation and antioxidant defense, which in turn seems to play a crucial role in the development of stroke. Furthermore, adherence to the Mediterranean diet has been linked to lower systolic and diastolic blood pressure and lower likelihood of hypertension [35–37], which is the most important modifiable cardiovascular risk factor for developing both ischemic and hemorrhagic stroke, as well as small vessel disease. Therefore, according to current analysis greater adherence to the Mediterranean diet was associated with 32% lower risk of stroke events and this could be partly attributed to the properties of this pattern mentioned above. Accordingly, adherence to the DASH dietary pattern has been proven to be effective as first-line therapy in individuals with stage I isolated systolic hypertension [24], but has been also associated with lower inflammation in patients with type 2 diabetes and in adolescents with metabolic syndrome [38,39]. Based on current evidence regarding the risk for stroke, the DASH dietary pattern is an alternate dietary pattern that can lower the risk for stroke both in hypertensive and healthy individuals.

Adherence to healthy dietary patterns could also affect the incidence of stroke by affecting other modifiable risk factors, namely obesity, diabetes and dyslipidemia. Indeed, according to a meta-analysis, the Mediterranean dietary pattern was proven to be more effective than low-fat diets in inducing clinically relevant long-term changes in the above mentioned cardiovascular risk factors [40] and there is also limited data supporting that also adherence to DASH-like diets protect against excessive body weight, type 2 diabetes and dyslipidemia [41,42].

As already mentioned, it has been suggested that up to 80% of stroke events could have been prevented [2] and according to data presented in the present review, adherence to dietary patterns such as the Mediterranean or the DASH diet can essentially contribute to stroke prevention. Given that compliance rates to the DASH diet are low, even in hypertensive subjects [43], and that during the past few decades, there has been a gradual abandonment of the Mediterranean diet by the inhabitants of the Mediterranean basin [44,45], primary prevention of stroke should incorporate dietary strategies and interventions aiming at increasing adherence to dietary patterns such as the Mediterranean, the DASH or other plant based patterns, taking into account local resources and traditions. Moreover, well-designed clinical trials are needed to test compliance to dietary patterns against stroke in high risk individuals, and contribute to the developing of prevention recommendations based on understandable for the general public dietary patterns.

Contributors

Meropi D. Kontogianni: performed literature search, and wrote the paper. Demosthenes B. Panagiotakos: performed the re-meta-analysis and wrote the paper.

Competing Interest

The authors declare no conflict of interest.

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