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DIET AND PRIMARY PREVENTION OF STROKE: SYSTEMATIC REVIEW AND DIETARY RECOMMENDATIONS BY THE *AD HOC* WORKING GROUP OF THE ITALIAN SOCIETY OF HUMAN NUTRITION

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ABSTRACT

Background and aims: To systematically review the latest evidence on established and emerging nutrition-related risk factors for incidence of and mortality from total, ischemic and haemorrhagic strokes.

The present review was conducted in the framework of the work carried out through 2015 and 2016 for the preparation of the Italian Guidelines for the Prevention and Treatment of Stroke, 8th Edition, by ISO-SPREAD (Italian Stroke Organization and the Stroke Prevention and Educational Awareness Diffusion).

Methods and Results: Systematic review of articles focused on primary prevention of stroke published between January 2013 to May 2016 through an extensive search of the literature using MEDLINE/PUBMED, EMBASE and the Cochrane Library. Articles were ranked according to the SIGN methodology while the GRADE system was used to establish the strength of recommendations.

As a result of our literature search, we examined 87 meta-analyses overall (mainly of prospective studies), a few isolated more recent prospective studies not included in the meta-analyses, and a smaller number of available randomized controlled trials and case-control studies. Based on the analysis of the above articles, 36 Syntheses of the available evidence and 36 Recommendations were eventually prepared.

The present document was developed by organizing the available evidence into three individual areas (nutrients, food groups and dietary patterns) to provide a systematic and user-friendly overview of the available evidence on the relationship between nutrition and primary prevention of stroke. Yet analysis of foods and food patterns allowed translating the information about nutrients in a tool more amenable to use in daily life also in the light of the argument that people eat foods rather than nutrients.

Conclusions: The present literature review and dietary recommendations provide healthcare professionals and all interested readers with a useful overview for the reduction of the risk of total, ischemic and haemorrhagic stroke through dietary modifications.

INTRODUCTION

Of the 17.5 million deaths attributable to cardiovascular disease, an estimated 6.7 million are due to stroke, which is among the top causes of death and disability worldwide [1,2].

In Europe, stroke by itself ranks as the second single most common cause of death accounting for almost 1.1 million deaths each year [3].

Considerable differences in stroke incidence were found across European countries with lower rates of total stroke observed in southern and higher rates in eastern European countries, especially in women [4] and death rates from stroke being much higher in Central and Eastern Europe than in Northern, Southern and Western Europe [3].

Stroke is estimated to cost the EU economy over €38billion a year, around one-fifth of the overall cost of CVD. Of the total cost of stroke in the EU, around 50% is due to direct health care costs, 22% to productivity losses and 29% to the informal care of people with stroke [3].

Despite the noticeable advancements in the treatment of patients with acute ischemic stroke, primary prevention remains the best approach for reducing the burden of stroke especially in light of the fact that 77% of strokes are first events [5].

Modifiable risk factors such as suboptimal systolic blood pressure (> 115 mmHg), excess salt intake, low fruit and vegetable consumption and physical inactivity have been identified as major contributory factors leading to an increase in stroke risk [6,7].

A landmark case-control study involving 22 countries worldwide found that ten modifiable risk factors explained up to 90% of the risk of stroke thus highlighting the need for targeted preventive strategies to substantially reduce the burden of stroke [8].

The tremendous impact of dietary habits as well as of single nutrients on the development of cardiovascular disease is well established; it has been estimated that a healthy dietary pattern based on the Dietary Guidelines for Americans may help to reduce by 30% the risk of coronary heart disease [9]. In the landmark PREDIMED trial, a Mediterranean-type of diet supplemented with extra-virgin olive oil or nuts was associated with a 29%% (HR:0.71; 95%CI 0.56–0.90) reduction in

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the rate of cardiovascular events and 39% (HR:0.61; 95%CI 0.44–0.86) lower rate of stroke compared with the low fat control diet in multivariate analysis [10].

The cardiovascular advantages deriving from adoption of a Mediterranean-like healthy diet were observed also for secondary CVD prevention [11].

To date, a persuasive body of evidence suggests that healthy dietary patterns - typically encouraging the consumption of adequate amounts of fruits, vegetables, legumes, non-refined cereals, fish and lower intake of animal foods – represent an optimal tool for stroke prevention, at least in part because of their favorable action on major risk factors for stroke (i.e. high blood pressure, high serum cholesterol and hyperglycemia) [12,13].

Yet the influence of diet and of specific nutrients in the primary prevention of stroke needs to be further explored, especially for hemorrhagic stroke for which the evidence is scarce and inconclusive.

The present document systematically reviews the latest evidence on established and emerging nutrition-related risk factors for stroke morbidity and mortality, with the purpose of providing healthcare professionals and individuals with evidence-based recommendations for the reduction of the risk of total, ischemic and hemorrhagic strokes through dietary modifications. It stems from the work carried out through 2015 and 2016 for the preparation of the Italian Guidelines for the Prevention and Treatment of Stroke, *8th Edition*, by ISO-SPREAD (*Italian Stroke Organization and the Stroke Prevention and Educational Awareness Diffusion*).

METHODS

As a contribution to the Guideline preparation, on December 2014, the Italian Society of Human Nutrition (SINU) was requested to appoint an *ad hoc* Working Group (WG) for Nutrition and Stroke* *(see appendix 1).* The Group identified the *nutritional risk factors for stroke* and defined *nutritional strategies for stroke prevention, nutritional care of the patient in the acute phase and*

nutritional care of the patient in the rehabilitation phase of stroke as the issues to be dealt with by the WG. For each of these issues the WG has delivered its conclusions to ISO-SPREAD in the form of specific Syntheses and Recommendations, which have been incorporated and make integral part of the ISO-SPREAD Guidelines [14].

The present article is an extensive report of the work carried out by the Nutrition and Stroke WG concerning the issue of Nutrition and Stroke Prevention and provides the rationale and the scientific bases of the nutritional recommendations for the prevention of stroke as delivered in the ISO-SPREAD Guidelines.

In the first place, the Group defined the work methodology and the distribution of the different tasks among its components. In accordance with the choice collectively made by the larger ISO-SPREAD Group, the WG on Nutrition and Stroke has adopted the SIGN methodology [15] in keeping with the previous editions of the guidelines. This methodology is based on the formulation of a comprehensive judgment of the evidence available for any given topic, i.e. on an objective appraisal of the quality and relevance of the studies available and not just of the statistical significance of their respective results. Following the new recent policy of SIGN, the ABCD method, used in the previous editions of the ISO-SPREAD guidelines to indicate the strength of the recommendations, was replaced by a simplified version of the GRADE system leading to the formulation of *strong* or *weak* recommendations in *favor* or *against* a given intervention: the decision was made on the basis of the quality, consistency and scientific value of the evidence available as well as of the assessment of the balance between the demonstrated advantages and possible adverse effects of a given factor [16]. The SIGN classification of the evidence and the GRADE assessment of the strength of recommendations are provided in Table 2.

The SIGN methodology was also adopted for the critical evaluation of the individual studies available on each topic, a *Study checklist* being compiled by a member of the WP to assess the internal and external validity of each of the available studies and to formulate a final global evaluation of its scientific value. Different checklists were used according to the type of study,

whether systematic review/meta-analysis, randomized controlled trial, prospective observational investigation, or case-control study [15]. For each topic, a final "C*onsidered judgment form*" was compiled by collecting all the information included in the studies check lists, thus coming to a global assessment of the scientific reliability and relevance of the studies available, the consistency of their results, the probability of publication bias, the apparent or possible benefits and harms of the intervention(s) proposed as well as the degree of feasibility and the predicted impact of the intervention on the population. Eventually, the considered judgment forms were used to prepare a SYNTHESIS of the relevant information on each selected topic and to deliver one or more specific RECOMMENDATIONS.

In summary, the process flow chart was made of the following steps:

1. Identification of the topics relevant to the formulation of the nutritional guidelines for stroke prevention;

2. Definition and implementation of the evidence search strategy;

3. Evaluation of the relevant articles and preparation of the respective check lists;

4. Preparation of the Considered judgment forms;

5. Preparation of the SYNTHESES of the available evidence and of the respective RECOMMENDATIONS;

6. Decision about level of evidence for each synthesis and strength of the individual recommendations.

We built up an archive, made up initially of all the relevant references retrieved for the previous editions of the ISO-SPREAD guidelines (the last one in 2012) and we integrated it with all the relevant articles gathered through an extensive search of the literature using MEDLINE/PUBMED, EMBASE and the Cochrane Library through November 2015. Additional information was retrieved through a manual search of references from recent reviews and relevant published original studies. The search of the databases was updated on May 30, 2016 to identify any new studies.

The key words used for our literature exploration were (in alphabetical order): alcohol, antioxidants, calcium, carbohydrates, cereals, cerebrovascular disease, coffee, chocolate, dairy products, DASH diet, diet, dietary patterns, egg, fat, fatty acids, fiber, fish, folate, fruit, magnesium, meat, Mediterranean diet, milk, minerals, nutrition, nuts, olive oil, potassium, proteins, sodium, stroke, stroke prevention, sweetened beverages, tea, vegetables, vegetarian diet, vitamins (an example of the search strategy is provided in Table 1).

As a result of this collaborative work, 36 SINTHESES and 36 RECOMMENDATIONS were eventually prepared: their formulation is the result of the examination of 87 meta-analyses overall (including mainly prospective and to a much smaller extent case-control studies and randomized controlled trials), of a few isolated more recent prospective studies not included in the meta-analyses, and of a smaller number of available randomized controlled trials and case-control studies.

Each synthesis or recommendation was initially prepared by 2-3 members of the WG and was then brought to the collective evaluation and judgment of the whole group. The group has held three ad hoc meetings at approximately three month intervals during 2015 for methodological confrontation and discussion of progress results. Eventually, all the syntheses and recommendations received the group general approval.

The present document was developed by organizing the available evidence into three individual areas (nutrients, food groups and dietary patterns) to guarantee an accurate scientific overview able to provide health researchers with consistent knowledge on the existing relationship between nutrition and primary prevention of stroke. Yet analysis of foods and food patterns allows translating the information about nutrients in something more amenable to use in daily life also in the light of the argument that people eat foods rather than nutrients.

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MICRONUTRIENTS

Sodium chloride (salt)

While a clinically relevant food deficit of sodium (and chlorine) is extremely unlikely in healthy individuals, excess in sodium chloride intake is extremely common and is a recognized causative factor of hypertension and of cardiovascular diseases [17-19]. Several meta-analyses of randomized controlled trials support the blood pressure lowering effect of reduction in sodium chloride intake [20, 21] and therefore it is realistic to expect that reduced salt intake favorably affects stroke risk. The biological plausibility of the association between sodium chloride intake and stroke risk is based on studies in genetic models of hypertensive rat consistently showing that elevated sodium chloride intake induced the development of vascular damage and led to an elevated incidence of stroke [21]. Moreover, both in vitro and clinical studies indicated that a higher plasma sodium concentration and/or an elevated sodium chloride intake negatively affect endothelial function [22, 23], oxidative stress [24], platelet aggregation [25], arterial stiffness [26, 27], left ventricular mass and function [28, 29].

After the meta-analysis by Strazzullo et al in 2009, two further meta-analyses have been published until 2015 [30]. The meta-analysis by Aburto et al. included nine studies with 14 comparisons and 72,878 individuals from general population samples [31]. Higher compared with lower salt intake was associated with a 24% (95% CI 8% to 43%; I^2=49%) higher rate of stroke.

The meta-analysis by Graudal et al. in addition to general population samples also included studies in high cardiovascular risk individuals or patients with clinical cardiovascular disorders [32]. The comparison of high (estimate of >215 mmol/day) vs usual sodium intake (115-215 mmol/day) with 7 studies and 186,091 individuals yielded a 21% higher rate of stroke in the first group (95% CI 4% to 41%), whereas the comparison of low (<115 mmol/day) sodium vs usual sodium again with 7 studies 56,582 subjects did not show a significant difference. This study however has been criticized because of inadequate assessment of salt intake and of high risk of reverse causality due to the inclusion of cohorts of seriously ill patients under intensive medical treatment [33].

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Summary of evidence

The vast majority of the available evidence indicates that elevated salt intake is associated with higher stroke risk, mainly but not exclusively, in force of its blood pressure raising effect. Few data are available to conclusively discriminate between ischemic and hemorrhagic subtypes. Although results from RCTs are lacking, the bulk of evidence derived from experimental, clinical and epidemiological studies and in particular the documented effect of excess salt intake reduction on blood pressure in both hypertensive and normotensive individuals, strongly suggest the need to reduce sodium chloride intake based on WHO recommendation [34]. In accordance with WHO recommendation, the 2014 revision of the Italian Reference Dietary Intakes (LARN) recommends 5 g of salt (2g of sodium) as the SDT (standard dietary target) for the population: this choice is mainly motivated by the results of randomized controlled trials indicating a linear decrease in blood pressure upon reduction of dietary sodium intake to values below 2 g/day [35,36].

Potassium

An inverse relationship between dietary potassium (K) intake and blood pressure has been reported both within and across populations [37-40]. Because hypertension is the leading cause of cerebrovascular disease [41], it is realistic to expect that higher K intake may affect stroke risk. Indeed, many milestone studies in animal models suggested that a high K intake reduces vascular damage and counteract the increase in stroke rates caused by a high Na regimen [42-46], even independently from the effect on BP.

An original observational investigation carried out in the eighties and including 859 men and women showed that stroke mortality was significantly lower among participants in the upper tertile of habitual dietary K intake after a 12-year follow-up observation [47]. Since then, a number of prospective studies have explored the possible association between dietary K intake and incidence of cerebrovascular events. A remarkable number of cohort studies and five systematic reviews and meta-analyses of these studies carried out on samples of adult general population have consistently

shown an inverse significant association between habitual K intake and risk of stroke [40, 48-51]. In a comprehensive analysis, including 14 cohorts from 12 prospective studies, based on 333,250 people and more than 10,600 stroke events an average weighted difference of 1500 mg per day in K intake was associated with a 20% lower risk of stroke (RR:0.80; 95% CI: 0.72-0.90; $I^2 = 47\%$) [50]. This inverse association was also detected in two dose-response analyses showing that an increase of 1,000 mg per day in dietary K intake was linearly associated with 10% (RR=0.90, 95%CI 0.84-0.96;I^2=47%) [50] and 11% lower risk of stroke (RR= 0.89, 95% CI, 0.83-0.97; I^2=50.8%) [49]. The analysis of stroke sub-types, although including fewer cohorts, confirmed a significant inverse association with ischemic (RR: 0.89; 95% CI= 0.81-0.97) but not with hemorrhagic stroke (intracerebral hemorrhage: RR: 0.95, 95% CI= 0.83-1.09; subarachnoid hemorrhage: RR: 1.08, 95% CI= 0.92-1.27) [49]. More recently, such results have been confirmed in the framework of the Women Health Initiative [52] and by the further meta-analysis by Vinceti and co-workers, which has shown in addition that, even for the risk of hemorrhagic stroke, the inverse relationship with potassium intake is statistically significant provided data unadjusted for blood pressure are used in the calculation [53]. This approach appears to be sound as the rate of hemorrhagic stroke is strongly dependent on blood pressure with consequent risk of overadjustment if adjustment for blood pressure is made.

Potassium supplementation

Few studies provided data on the relationship between supplemental K and stroke risk. In a large cohort of men, K supplementation was associated with reduced risk of total stroke [51], whereas, in a previous analysis, a similarly favorable effect was detected mainly among hypertensive male participants [52]. A similar trend not achieving statistical significance was further observed in a recent analysis of the Nurses' Health Study database with regard to ischemic stroke [54].

Summary of evidence

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A large body of evidence supports a favorable effect of dietary K intake on stroke risk, also in part independently of its well-recognized beneficial effect on BP, although few data are available to conclusively discriminate between ischemic and hemorrhagic subtypes or in favor of K supplementation.

The 2014 Revision of the Italian Dietary Reference Intakes (LARN) set a value of 3900 mg a day as a potassium adequate intake for the adult population, in accordance with other similar documents released by European and American authorities, also based on the potassium content of 4200 mg/day of the DASH diet which was shown to be effective in lowering blood pressure in a controlled dietary intervention trial [55].

<u>Calcium</u>

The relationship between calcium intake and stroke has been explored by many prospective studies. The majority of them addressed calcium intake from food as a whole or by comparison of dairy versus non-dairy calcium intake. A few other studies focused on the association between supplemental calcium intake and stroke.

Total dietary calcium intake and stroke

In their meta-analysis of 11 observational prospective studies with 436,150 participants and 9,095 strokes, Larson and colleagues assessed the dose-response relationship between total dietary calcium intake and risk of stroke [56]. Because of the significant heterogeneity observed among all studies ($I^2 = 70.3\%$), the authors stratified the analysis by population average calcium intake (<700 mg/day vs. >700 mg/day). Dietary calcium intake was inversely associated with risk of stroke in populations with an average calcium intake <700 mg/day (RR for a 300-mg/d increase in calcium intake: 0.82; 95% CI 0.76-0.88; I^2=0.0%). On the contrary, it was weakly positively associated with stroke risk in populations with a calcium intake >700 mg/day (RR: 1.03; 95% CI 1.01-1.06; I^2=0.0%). An inverse association between calcium intake and risk of stroke was actually apparent only in Asian populations, which had in general a relatively low calcium intake (RR for an increase

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of 300 mg/d in calcium intake: 0.78, 95% C.I. 0.71-0.87): there was however some evidence of possible publication bias [56].

In another meta-analysis of 10 prospective studies with 371,495 participants and 10,408 strokes, Tian and colleagues did not detect an association between calcium intake and risk of total stroke (RR: 0.96; 95% CI 0.89-1.04; I^2=66.3%) or of any stroke subtype. However, in a separate analysis of seven studies with follow-up longer than 14 years, high calcium intake was indeed associated with reduced stroke rate (RR: 0.67; 95% CI 0.51-0.88; I^2=0.0%) [57].

Finally, in a very recent meta-analysis including 20 cohort studies, dose–response meta-regression analysis did not find statistically significant linear or nonlinear relationships between levels of dietary or total calcium intake and the risk of total stroke or stroke mortality [58].

Dairy vs. non-dairy calcium intake

Analyzing the relationship between dairy and non-dairy calcium intake and stroke, Larson and colleagues reported that the RR of stroke for a 300-mg/day increase in calcium intake was 0.78 (95% CI 0.62-0.99) for dairy calcium and 0.98 (95% CI 0.73-1.30) for non-dairy calcium [56]. The addition of another study providing results for only dairy calcium intake did not change the results (RR: 0.73; 95% CI 0.59-0.91) [59]. In their updated meta-analysis, also Tian and colleagues found that high dairy calcium intake was associated with a 24% reduction in the risk of total stroke (RR: 0.76; 95% CI 0.66-0.86; I^2=0.0%), while non-dairy calcium intake had no effect (RR:0.99; 95% CI 0.84-1.16; I^2=33.3%)) [57].

Calcium supplements

While the meta-analyses of prospective studies indicate the absence of any significant correlation between calcium supplemental intake and stroke [56,57], a meta-analysis of nine intervention trials comparing administration of calcium with or without vitamin D vs. placebo (28,072 participants, 676 incident myocardial infarctions and 764 incident strokes, mean follow-up 5.7 years) showed

that the supplementation of calcium or calcium and vitamin D increased the risk of stroke (RR:1.15, 95%CI=1.00-1.32; I^2=0.0%), myocardial infarction (RR:1.24, 95% CI=1.04-1.45; I^2=0.0%) and the composite of myocardial infarction and stroke (RR:1.15, 95% CI=1.03-1.27; I^2=0.0%) [60].

Summary of evidence

In conclusion, while the evidence of a protective effect of calcium from dairy products on the risk of stroke is consistent, evidence of the impact of total calcium intake was detected only in populations with a lower than average calcium intake and in studies with a longer follow-up. On the other hand, the combined evidence of prospective observational studies and randomized controlled intervention trials indicates that calcium supplements may increase the risk of myocardial infarction and stroke. With respect to possible mechanisms of the effects of calcium and dairy intake on stroke risk, recent data from the ATTICA cross-sectional study of a sample of general population [61] and from a few randomized controlled trials in overweight individuals [62] suggest that consumption of dairy products is inversely associated with low-grade systemic inflammation. Moreover, a dose-response meta-analysis of prospective cohort studies indicated an inverse relationship of low-fat dairy and milk consumption to the incidence of hypertension [63].

Magnesium

Larson and colleagues in a meta-analysis of seven prospective studies recently explored the relationship between magnesium intake and stroke with 241,378 participants and 6477 events [64]. The authors found that total dietary magnesium intake was inversely associated with the risk of stroke, specifically ischemic stroke. In particular, an increment of 100 mg in magnesium dietary intake per day was associated with an 8% reduction in the risk of total stroke (RR: 0.92; 95% CI 0.88-0.97; I^2 = 0%). In a subsequent meta-analysis of 8 prospective studies with 304,551 participants and 8,367 events (same as for Larsson meta-analysis plus one new study), Nie and colleagues confirmed the significant inverse association between magnesium intake and risk of total

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stroke (RR: 0.89; 95% CI 0.82-0.97; $I^2 = 0.0\%$) [65]. Subgroup analyses suggested a significant inverse association between magnesium intake and the risk of ischemic stroke (RR: 0.88; 95% CI 0.80, 0.98). A few subsequent population-based cohort studies confirmed that a higher magnesium intake from food was associated with decreased risk of stroke. In particular, Sluijs et al. analyzing the European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) study cohort confirmed the association between high dietary magnesium intake and a reduced stroke risk [66]. As previously mentioned, the analysis of the Health Professionals Follow-up Study (HPFS) database performed by Adebamowo and coll. indicated that a diet rich in magnesium, potassium, and calcium contributes to reduced risk of stroke in men [51]. Again Adebamowo and colleagues, analyzing the Nurses' Health Study (NHS) I and II databases and performing a subsequent meta-analysis of prospective studies, found that a combined mineral diet with high intake of magnesium and potassium was associated with reduced risk of stroke (combined RR of total stroke = 0.87 (95% CI 0.83, 0.92) for a 100-mg/d increase of magnesium intake and 0.91 (95% CI 0.88, 0.94) for a 1000-mg/d increase of potassium intake; with no between-study heterogeneity) [54].

Summary of evidence

There is consistent evidence in favor of a protective effect of a higher intake of magnesium toward the risk of stroke, in particular of ischemic stroke.

Vitamins and antioxidants Literature data on stroke prevention are especially focused on B vitamins, including folate, vitamin B_6 and B_{12} (all involved in the metabolism of homocysteine, a potential risk factor for cardiovascular diseases) [67], as well as on vitamins counteracting oxidative stress and inflammation (both involved in the pathogenesis of cardiovascular diseases) [68, 69], namely vitamin A, C and E. Recently, besides its effect on bone health, vitamin D is also emerging as a factor involved in the modulation of a number of physiological processes such as the renin-

angiotensin system activity, endothelial function, vascular smooth muscle proliferation, insulin sensitivity, and systemic inflammation [70, 71].

Folate, Vitamin B$_6$, Vitamin B$_{12}$

These three vitamins are strictly connected in the one-carbon metabolic pathway in which homocysteine is a crucial metabolite that can accumulate either as a result of genetic defects or of nutritional deficiencies [67].

Several studies support the protective role of dietary folate against stroke, while data on vitamin B$_{12}$ and B$_6$ remain less clear. However, meta-analyses or systematic reviews on these topics are missing. A cohort study (9,764 healthy individuals, aged 25-74 y) showed reduced ischemic stroke incidence (RR:0.79; 95% CI 0.63-0.99) among individuals in the highest quartile of folate intake compared with those in the lowest quartile [72], a finding in accordance with results from an Asiatic population [73] in which low folate intake was associated with increased ischemic stroke risk (HR:1.61; 95% CI 1.04-2.48 and HR:1.82; 95% CI 1.20-2.76 for 1st and 2nd quartiles compared with 3rd and 4th quartile combined). In contrast, neither the cohort study of 83,272 US female nurses [74] nor the investigation on subjects from the Northern Sweden Health and Disease Cohort [75] found a relationship between folate intake, folate plasma levels or vitamin B$_{12}$ intake and stroke. In the Japan Collaborative Cohort Study (23,119 men and 35,611 women, aged 40-79 y), no association was found between vitamin B$_{12}$ intake and stroke mortality; high dietary folate (> 536 µg/d) and vitamin B$_6$ (> 1.33 mg/d) intakes showed a downward trend for mortality in women (HR: 0.83; 95% CI 0.61-1.12 for folate; HR: 0.63; 95% CI 0.39–1.03 for vitamin B$_6$) but not in men [76]. In a large cohort of US men (n= 43,732), He and colleagues detected an inverse relationship between folate or vitamin B$_{12}$ intakes and risk of ischemic stroke (RR: 0.71; 95% CI 0.52-0.96 for folate; RR: 0.73; 95% CI 0.53-0.99) [77]. Likewise, high dietary folate intake was linked to decreased risk of cerebral infarction (RR:0.80; 95% CI 0.70-0.91) in Finnish male smokers (n=26,556), especially among those with a high vitamin B$_{12}$ intake; nevertheless, vitamin B$_6$, vitamin B$_{12}$, and methionine

intakes alone were not associated with risk of stroke [78]. Despite the limited number of subjects (n= 967), the study by Weikert et al. detected a significant association between low vitamin B_{12} plasma levels and increased risk of cerebral ischemia, whereas the intake of folate and vitamin B_6 were not associated at all [79].

Folate, Vitamin B6, Vitamin B12 supplementation

Since 2012, nine meta-analyses of RCTs have been published on the effect of vitamin B supplementation on the risk of stroke. The majority of them showed a borderline reduction ranging between 9 and 6 % of the risk of stroke after vitamin B supplementation [80-85].

The meta-analysis by Zeng and co-workers studied the potential effect of folate supplementation on stroke risk by stratifying previous RCTs according to fortification status [86]. The final fourteen RCTs enrolled 39,420 patients (7 without folate fortification, 4 with folate fortification and 3 with partial folate fortification). The RR for stroke was 0.88 (95 % CI 0.77-1.00; I^2=1%) in the subgroup without folate fortification, 0.91 (95 % CI 0.82, 1.01; I^2=47%) in the subgroup with partial folate fortification and 0.94 (95 % CI 0.58, 1.54; I^2=61%) in the subgroup with folate fortification.

In the meta-analysis of Dong et al. a total of 17 trials (86,393 patients) comparing 7 treatment strategies with vitamin B (FA + VB_6 + VB_{12}, FA + VB_6, FA + VB_{12}, V_{B6} + VB_{12}, FA, VB_6, niacin and placebo] were included [87]. Supplementation with B vitamins was associated with reduced risk of stroke and cerebral haemorrhage (RR: 0.90; 95% CI 0.84-0.98; I^2=15.8% and 0.74; 95% CI 0.58-0.94; I^2=0.0%, respectively), but not of ischemic stroke (RR: 0.97; 95% CI 0.88-1.07; I^2=0.0%) in the standard meta-analysis. In the network meta-analysis, the risk of stroke was lower with folic acid plus vitamin B_6 as compared with folic acid plus vitamin B_{12} and was lower with folic acid plus vitamin B_6 plus vitamin B_{12} as compared with placebo or folic acid plus vitamin B_{12}.

Recently, in the meta-analysis by Li et al. of 30 RCTs involving 77,816 participants and 3,164 stroke events folic acid supplementation showed a relative risk for stroke of 0.90 (95% CI 0.84-0.96; I^2=27.4%) compared with controls [88]. The effect of intervention was more pronounced

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among participants with lower plasma folate levels at baseline (RR: 0.79, 95% CI 0.69–0.89 *vs* RR: 0.97, 95% CI 0.86–1.08, for baseline folate <16 nmol/L and ≥16 nmol/L, respectively, P=0.02 for interaction)-.

Summary of evidence

So far, studies on the impact of dietary vitamins B_6 and B_{12} on the risk of stroke are few and controversial. Conversely, there is evidence of a protective effect of regular consumption of high folate-containing foods although this effect may be attributable, at least in part, to other beneficial nutrients, namely vitamin C, phytochemicals, fiber also present in plant foods. Systematic supplementation of folic acid, vitamin B_6 or vitamin B_{12} (alone or in combination) shows a slightly beneficial effect on primary prevention of stroke, more so in subjects with lower levels of folate.

Vitamin A, Vitamin C, Vitamin E

Up to now, only few literature data on antioxidant vitamins and stroke are available. Reliable studies only concern vitamin C and its potential mechanisms of action (prevention of endothelial dysfunction, anti-inflammatory and anti-hypertensive role) [89, 90]. A meta-analysis including 11 prospective studies on vitamin C intake (217,454 participants and 3,762 stroke events) and 6 prospective studies on plasma vitamin C levels (29,648 participants and 989 stroke cases) demonstrated that both dietary intake and plasma levels of vitamin C were inversely related to the risk of stroke, in a dose-dependent manner (RR:0.81; 95% CI 0.74-0.90; I^2=0.0% for dietary vitamin C intake and RR:0.62; 95% CI 0.49-0.79; I^2=27.6% for circulating vitamin C high-versus-low categories) [91]. The RR for each 100 mg/day increment in dietary vitamin C was 0.83 (95% CI 0.75- 0.93), and for each 20 nmol/L increment in circulating vitamin C was 0.81 (95% CI 0.75 to 0.88; I^2=0.0%).

In contrast, a meta-analysis of 15 randomized controlled trials (188,209 participants and 3,749 stroke events) concluded that antioxidant vitamin supplementation had no effects on the rate of cardiovascular events, including stroke (RR:0.99; 95% CI 0.93–1.05; I^2=0.0%) [92].

Two large studies failed to demonstrate any association between vitamin A or vitamin E intake and incidence of stroke or stroke mortality [93, 94]. However, high vitamin E intake was associated with increased risk of haemorrhagic stroke (HR: 2.94, 95% CI 1.13-7.62) [94].

Summary of evidence

A diet rich in vitamin C appears to be beneficial for the prevention of ischemic stroke whereas there is no apparent association between vitamin A or vitamin E intake and stroke rates. Both randomized controlled trials and meta-analyses thereof provide no support for the use of antioxidant vitamin supplements in the prevention of stroke.

Vitamin D

A large body of evidence points to the renin-angiotensin system activity, endothelial function, smooth muscle proliferation, insulin sensitivity and systemic inflammation as possible targets of the vitamin D biological system for the prevention of cardiometabolic disorders, including stroke [95].

Dietary vitamin D and vitamin D supplementation

The contribution of vitamin D intake from foods or supplements to cardiovascular health is still controversial (very likely because 80% of the vitamin requirement is covered by sun exposure and because other confounding factors exist), even though two cohort studies suggest a potential beneficial effect. In the Honolulu Heart Program, it was shown that low dietary vitamin D intake was associated with an increased risk of stroke and, in particular, thromboembolic stroke in Japanese-American men [96]. On the other hand, in a meta-analysis of 21 trials with 13,033 participants, evaluating the effect of vitamin D supplementation (in the form of cholecalciferol, calcitriol, ergocalciferol or vitamin D analogs) on the risk of cardiovascular events, Ford et al. [97] did not detect any association between vitamin D supplementation and risk of stroke (RR: 1.07; 95% CI: 0.91-1.29).

Summary of evidence

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There is consistent evidence that low circulating levels of vitamin D are associated with an increased risk of stroke, while still sparse are the data on the association between dietary intake of vitamin D and stroke. There is no convincing evidence however of a significant effect of vitamin D supplementation on the rate of stroke.

Dietary Fiber

Dietary fiber has been reported to reduce the risk of hypertension, the strongest risk factor for stroke [28], to positively affect LDL-cholesterol, postprandial lipids levels and insulin sensitivity [98, 99], fibrinolysis [100] and inflammation [101].

In the last few years three meta-analyses were published that evaluated the association of dietary fiber intake and stroke risk. The meta-analysis by Chen and coworkers included six prospective cohort studies for a total of 314,864 participants and 8920 stroke cases [102]. The analysis showed that the RR of stroke was 13% lower (RR: 0.87; 95% CI 0.77-0.99; I^2=36.4%) in the highest vs lowest category of dietary fiber intake. Subgroup analysis indicated that the RR for men and women were 0.95 (95% CI, 0.83-1.08) and 0.80 (95% CI, 0.66-0.96), respectively, and that the RR for ischemic stroke and hemorrhagic stroke were 0.83 (95% CI, 0.72–0.96) and 0.86 (95% CI, 0.70–1.06), respectively, although the analysis on stroke subtypes was based on a quite small number of studies. Dose-response analysis suggested a 12% reduction in stroke risk for each 10g/day increment in dietary fiber intake.

The meta-analysis by Threapleton and coworkers including two additional studies to those evaluated by Chen [102], with 2781 incident stroke events, showed that a 7g/day increase in total fiber intake was associated with 7% reduction in total stroke risk (RR: 0.93; 95% CI, 0.88–0.98; I^2=59%) [103]. There was no statistical evidence of an association between higher (4g/day) soluble fiber intake and risk of stroke. The meta-analysis of Zhang and coworkers included 11 prospective cohort studies and 325,627 participants [104]. The meta-analysis evaluated the relation of dietary

fiber intake, fiber source and type of fiber with the risk of fatal and nonfatal stroke. It showed that the relative risk of stroke was lower by 17% (RR: 0.83; 95% CI 0.74-0.93; $I^2 =$ 38.7 %) in the highest vs lowest category of dietary fiber. Moreover, a dose–response association between dietary fiber intake and stroke risk was observed. In particular, there was a reduction of 10%, 16% and 23% for 5g, 10g and 15g increments in fiber intake, respectively. However, dietary fiber intake was not related to stroke mortality. In subgroup analyses, greater dietary fiber intake was inversely associated with the risk of ischemic stroke (RR: 0.83; 95% CI 0.74-0.93; $I^2=20.5\%$) while a trend of protection for hemorrhagic stroke was observed (RR: 0.87; 95% CI 0.72-1.05; $I^2=0.0\%$). Both cereal and vegetable fibers were associated with reduced stroke risk by 24% and 14%, respectively, whereas no association was reported for fruit fiber and for soluble and insoluble fiber intake.

Summary of evidence

The results of the three available meta-analyses of prospective studies consistently indicate that the consumption of dietary fiber is dose-dependently associated with a lower risk of stroke. The beneficial effect seems to be greater for ischemic than for hemorrhagic stroke. It also seems more pronounced for cereal and vegetable fiber intake.

MACRONUTRIENTS

Carbohydrates

Postprandial hyperglycemia is an independent risk factor for stroke. Dietary carbohydrate (CHO) is the main factor able to influence the blood glucose response. The glycemic index (GI) of a food, an index of CHO quality, is commonly used as marker of the postprandial blood glucose response [105]. In addition, given that the amount and the quality of carbohydrates in the diet is extremely variable and thus may have a variable influence on the postprandial glycemic response, the glycemic load (GL) (calculated as the product of the GI of a food item and its available carbohydrate content) is widely used to assess the glycemic effect of CHO rich foods [106].

Carbohydrates, GI and GL

The possible associations between CHO intake/GI/GL and stroke risk were evaluated in two meta-analyses. The first one, including 6 prospective cohort studies, showed that a high GL was associated with an increased risk of total stroke (RR: 1.19; 95%CI 1.00-1.43; I^2=0.0%) whereas a high GI was not associated with risk of stroke or stroke-related death (RR: 1.09; 95%CI 0.94-1.26; I^2=0.0%) [107]. Similar results were reported in the meta-analysis by Cai and coworkers that included seven prospective studies [108]. In this meta-analysis on 225,000 participants free from diabetes, high CHO intake and high GI were not associated with stroke (RR: 1.10; 95%CI 0.99-1.21; I2=23.0% and RR: 1.12; 95%CI 0.95-1.35; I^2=6.3%, respectively) while a high GL was associated with an increased risk of stroke, (RR: 1.19; 95%CI 1.05-1.36; I^2=5.0%). No information on the possible association of high CHO intake/GI/GL with different subtypes of stroke was provided.

The mechanism whereby a high GL would increase stroke risk may consist in the vascular injury induced by a chronic increase in blood glucose and postprandial insulinemia, both of which act through a higher oxidative stress and sub-clinical systemic inflammation with production of oxidized lipoproteins and AGEs [109, 110].

Summary of evidence

The results of the two meta-analyses of prospective cohort studies indicate that high dietary GL is directly associated with the risk of stroke while CHO intake and GI are not. These findings support recommendations for decreasing daily consumption of high GI foods/diet to prevent stroke.

Fatty acids

Monounsaturated fatty acids (MUFA)

There is clinical and epidemiological evidence that dietary MUFA may help lower blood pressure [111], reduce low-density lipoprotein cholesterol and triglyceride [112], and thus lower estimated cardiovascular risk. Over the past 20 years, the analysis of cohort studies of MUFA intake in relation to primary prevention of stroke has yielded however inconsistent results, possibly due to the different dietary sources of MUFA.

One meta-analysis reviewing the literature until June 2014 (11 cohort studies on combined MUFA, olive oil, oleic acid, and MUFA:SFA ratio and 9 studies on MUFA intake only) indicated that top versus bottom third combined MUFA, olive oil, oleic acid, and MUFA:SFA ratio was associated with a reduced risk of stroke (RR:0.83, 95% CI 0.71-0.97; $I^2 = 70\%$) [113]. Subgroup analysis showed that actually olive oil intake was most likely crucial for this result, since higher intakes of olive oil were associated with reduced risk of stroke (RR:0.60, 95% CI 0.47-0.77; $I^2=0.0\%$). In contrast, the association between monounsaturated fatty acid intake of mixed animal and plant origin and stroke risk did not attain statistical significance although exhibiting a trend for protection (RR: 0.85, 95% CI 0.72-1.01; $I^2 = 65\%$).

Consistently, a more recent meta-analysis of 10 prospective cohort studies, including 314,511 individuals and 5827 strokes, provided evidence that high MUFA intake was borderline associated with the overall risk of stroke (RR:0.86, 95% CI 0.74-1.00; $I^2=48\%$) [114]. Subgroups analysis showed that higher dietary MUFA intake was inversely associated with the risk of hemorrhagic (RR: 0.68, 95% CI 0.49-0.96; $I^2=0.0\%$) but not of ischemic stroke (RR: 0.92, 95% CI 0.79-1.08; $I^2=41\%$).

Saturated fatty acids (SFA)

A meta-analysis of eight prospective cohort studies, including 179,436 subjects, did not show a significant association between SFA intake and risk of stroke (RR: 0.81, 95% CI 0.62-1.05; I^2=61%) [115].

Another meta-analysis of 13 observational studies [116] also showed that SFA intake was not associated with ischemic stroke (RR: 1.02, 95% CI 0.90-1.15; I^2=59%).

A very recent meta-analysis including two more studies, for a total of 476,569 individuals and 11,074 strokes, concluded that apparently higher SFA intake was associated with reduced risk of overall and fatal stroke (RR:0.89, 95 % CI 0.82-0.96; I^2=37.4% and RR: 0.75; 95 % CI. 0.59–0.94; I^2=0.0%, respectively) [117] but in subgroup analysis the association was present only for East-Asians (I^2=42.4%), for a SFA amount <25 g/day (I^2=45.3%), for men (I^2=0.0%) and for a BMI<24 (kg/m$^{2;}$ I^2=34.1%).

Only one meta-analysis examined randomized controlled trials of at least 6 months duration reducing or substituting saturated fat with other types of fat [118]. The overall assessment of ten such trials, involving 25,063 subjects randomized to reduced/modified diet and 34,790 subjects to usual diet, showed a RR for any type of stroke of 0.99 (95% CI 0.89-1.11; I^2=0.0%).

Trans unsaturated fatty acids (TFA)

The meta-analysis by De Souza et al. also examined the possible association of TFA intake with cardiovascular disease [116]. Only three studies with 1,905 cases out of 190,284 participants analyzed the association between TFA intake and ischemic stroke, showing a non-significant RR of 1.07 (95% CI 0.88-1.28; I^2=67%) with a considerable heterogeneity among studies.

Polyunsaturated fatty acids (PUFA)

Much more explored was the association between stroke and PUFA intake or PUFA blood levels with eight meta-analyses published in the last 5 years. Chowdhury et al analyzed 14 population based prospective studies of the relationship between long chain omega 3 fatty acids (LCn-3FA) and the risk of cerebrovascular events, involving 305,119 participants and 5374 strokes [119]. Ten

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studies dealt with dietary PUFA intake and four with PUFA blood levels: in both cases no significant associations were detected (RR:0.90, 95% CI 0.80-1.01;I^2=18% and RR:1.04, 95% CI 0.90-1.20; I^2=0.0%, respectively): this was true for both ischemic and hemorrhagic stroke types.

In the meta-analysis by Larsson et al [120] including 8 prospective studies with 5,238 stroke events among 242,076 participants, there was likewise no overall significant association between intake of LCn-3FA and total stroke risk although a trend for protection was observed (RR: 0.90, 95 % CI 0.81–1.01; I^2=13.9%).

The meta-analysis by Pan et al. focused on the plant-derived omega-3FA α-linolenic acid (ALA; 18:3n23) [121]. The authors reviewed 5 prospective studies (100,915 participants, 3026 cases), that assessed either dietary ALA intake or ALA biomarker concentrations. Neither dietary ALA (RR: 0.96, 95% CI 0.78-1.17; I^2=49.7%) nor ALA blood levels (RR: 0.77, 95% CI 0.37-1.60; I2=74.6%) were associated with the risk of stroke.

In a more recent cohort study, Mozaffarian et al. reported that total plasma phospholipids LCn-3FAwere inversely related to ischemic stroke risk with a 37% lower risk in the highest versus the lowest quintile but without significant relationship with hemorrhagic stroke [122].

A number of trials were performed to test whether LCn-3FAsupplementation would reduce the incidence of cardiovascular accidents. In particular, five meta-analyses have reviewed randomized controlled trials of the effect of PUFA supplements on the risk of stroke. In the meta-analysis by Kotwal et al. [123], including 7 studies having stroke as an outcome with 46,750 participants and 1369 events, no association was detected between ω-3 FA supplementation and the rate of cerebrovascular events overall (RR: 1.03, 95% CI 0.92-1.16;I^2=9.3%). Likewise, in their meta-analysis of 7 randomized, double-blind, placebo-controlled trials, Kwak and coworkers detected no effect of EPA and DHA supplements on the incidence of stroke or transient ischemic attacks among patients with previous evidence of existing CVD (RR:1.13, 95% CI 0.77-1.66; I^2=31.1%) [124].

Similar results were provided by the meta-analysis of RCTs of EPA and DHA supplementation performed by Rizos et al. and including 9 studies with 1490 stroke events among 52,589 participants (RR: 1.05, 95% CI 0.93-1.18; I^2=14%) [125].

Chowdhury et al. meta-analyzed 12 randomized controlled trials of ω-3 FA supplementation with 62,040 participants and 1563 stroke events [119]. No significant effect was observed overall (RR: 1.03, 95% CI 0.94-1.12; I^2=3.5%), and so also for primary or secondary prevention trials as well as for ischemic or hemorrhagic stroke.

Summary of evidence

In conclusion, based on a large number of prospective observational studies and randomized controlled trials, there is no convincing evidence of an effect of different types of fatty acid intake, either as dietary intake or plasma level, on the risk of stroke. The apparent discrepancy between these studies results and those of studies focusing on foods containing such fats (olive oil, nuts, fish, meat, milk and dairy products) may be at least partly explained by the fact that the protective or harmful effect of a given food on human health is the result of a complex interaction among its micro- and macro-nutrient constituents.

Protein

The meta-analysis by Zhang et al. combined the results from seven prospective studies involving 254,489 participants [126]. The pooled RR for stroke for the highest compared with the lowest dietary protein intake was 0.80 (95% CI 0.66-0.99; I^2=61.1%). The dose-response analysis indicated that a 20-g/d increment in dietary protein intake was associated with a 26% lower risk of stroke. Upon stratification for type of protein, the RR for stroke for animal protein was 0.71 (95% CI 0.50-0.99; I^2=69.4%). However, a recently updated meta-analysis of 12 prospective studies with 528,982 participants showed no evidence of an association between total protein intake and stroke risk (RR 0.98; 95% CI 0.89–1.07; I^2=66.5%), whereas dietary vegetable protein intake was associated with a slight but significantly lower rate (RR 0.90; 95% CI 0.82–0.99; I^2=0.0%) [127].

Blood pressure-lowering might be a possible explanation for the association between dietary vegetable protein intake and the risk of stroke [128].

Summary of evidence

There is still insufficient evidence in support of an association between dietary protein intake and stroke.

1. FOOD GROUPS

Vegetable sources

Fruits and vegetables

The evidence in favor of a direct association between fruits and vegetables intake and the risk of stroke has been recently confirmed by a meta-analysis of 20 cohort studies by Hu D et al. who found that 200 g higher daily intakes of fruits or vegetables were respectively associated with 32% lower (RR: 0.68; 95%CI 0.56–0.82) and 11% lower (RR: 0.89; 0.81–0.98) rates of stroke [129]. The findings were consistent for ischemic (RR: 0.79; 0.74–0.85) and hemorrhagic stroke (RR: 0.78; 0.69–0.88). Data from the Japanese prospective study by Okuda et al. revealed a protection against stroke death of as much as 28% (HR: 0.72; 95%CI 0.54-0.95) for the highest vs the lowest quartile of fruit intake whereas no such association was found for vegetable consumption [130].

In the HAPIEE cohort study the highest intake of fruit and vegetable (corresponding to a daily median intake of 831g) reduced stroke mortality by 48% (HR:0.52; 95%CI 0.28–0.98) [131].

The possible protective effect of fruits and vegetables has indeed a strong biological basis. Fruits and vegetables are rich sources of potassium, magnesium, folate, fiber, and antioxidant compounds (vitamin C, beta-carotene, and flavonoids). Their effect can be mediated by reduction of blood pressure and improvement of microvascular function [132, 133].

Summary of evidence

The large majority of the available evidence is in favor of an inverse association between fruits and vegetables consumption and the risk of stroke.

Legumes

A meta-analysis by Afshin et al of 6 prospective cohort studies including a total of 254,628 participants and about 7,000 stroke events was not able to detect an association between legumes intake and risk of total stroke (RR: 0.98; 95% CI 0.84-1.14; I^2=32%) or stroke subtypes [134]. So also was a second meta-analysis of 8 prospective studies with a total of 468,887 subjects and 10,493 stroke events by Shi and coworkers (SRR: 0.95; 95% CI 0.84–1.08; I^2 = 43.2%) [135].

Summary of evidence

Based on the results of two meta- analyses, no association is apparent between legumes consumption and risk of stroke. This finding is unexpected considering that legumes are good sources of potassium, magnesium, fiber and vegetable protein and that they have been associated with documented benefits on several risk factors for stroke, i.e. hyperlipidemia [136], hyperglycemia [137] and high blood pressure [138], as well as on the risk of coronary heart disease [134].

Nuts

Overall 10 meta-analyses of mainly prospective observational studies and one randomized controlled trial have provided information about the relationship between nut consumption and risk of stroke over the last three years.

The meta-analysis by Afshin et al. of three prospective cohorts and one RCT for a total of 155,685 participants and 5,544 events failed to detect an association between nut intake and total stroke, although a trend toward protection emerged (RR: 0.89; 95% CI 0.74-1.05; I^2=72.7%), or stroke subtypes [134]. In a meta-analysis of 8 prospective studies with a total of 468,887 subjects and 10,493 stroke events Shi et al. reported a favorable effect of higher nut intake (RR: 0.90, 95% CI 0.81-0.99; I^2=0.0%) [135]. Gender was found to modify the effect of nut consumption on stroke

risk, with greater health advantages for women (RR: 0.85, 95% CI 0.75-0.97; I^2=0.0%) in comparison with men (RR:0.95, 95% CI 0.82-1.11; I^2=0.0%).

Luo et al. analyzed data from five studies and found a protection from stroke associated with high nut intake confined to women (RR: 0.87; 95% CI 0.77 -0.98; I^2=0.0%) [139]. The meta-analysis by Zhou et al. using data from four prospective studies including 182,730 participants and 5,669 stroke cases failed to find an association (RR: 0.90; 95% CI 0.71-1.14; I^2=49.6%) [140]. Likewise, in the meta-analysis by Grosso et al., based on only two cohort studies of nut intake and stroke mortality, higher nut consumption was not significantly associated with the rate of stroke death (RR:0.84; 95%CI 0.64-1.09; I^2=0.0%) [141].

On the other hand, Zhang et al. , on the basis of six studies including nine independent cohorts with 476,181 participants, estimated a reduction in the risk of stroke of as much as 10% (pooled RR: 0.90; 95% CI 0.83-0.98; I^2=0.0%) comparing the highest with the lowest nut consumption [142]. In line with previous evidence, this meta-analysis suggested health advantages for women (RR: 0.88; 95% CI 0.78-0.98; I^2=0.0%) but not for men (RR: 0.92; 95%CI 0.82–1.05; I^2=0.0%). In dose-response analysis overall an increment of 1 serving/day in nut consumption showed a trend for protection toward stroke risk (RR: 0.94; 95 % CI 0.82–1.08). Still more recently, Mayhew et al. reported no associations of higher nut consumption with ischemic (RR: 1.06; 95%CI 0.81-1.38; I^2=64%), hemorrhagic (RR: 0.83; 95% CI 0.59-1.16) or total stroke (RR: 1.05; 95%CI 0.69-1.61; I^2=77%) [143]. The authors found however a marginally significant reduction of 17% in the total stroke death rate (RR: 0.83; 95% CI 0.69-1.00; I^2=0.0%).

In the most recent dose-response meta-analysis of 14 cohort studies conducted by Shao et al. evidence for a nonlinear association between nut intake and stroke risk was observed with a RR of 0.86 (95%CI 0.79–0.94) for a 12 g/day greater nut consumption [144].

Finally, the PREDIMED randomized controlled trial showed that high cardiovascular risk individuals consuming a Mediterranean diet with one serving per day of mixed nuts (30 g) had a

46% reduced risk of stroke (HR: 0.54, 95%CI 0.35–0.84) as compared to a control group allocated to a lower fat control diet [10].

Summary of evidence

A reduction in stroke risk associated with greater consumption of nuts was documented in four meta-analyses of prospective studies and by one RCT; two meta-analyses showed health advantages confined to women, whereas four meta-analyses did not reveal any beneficial effect. Therefore, the evidence on the health advantages of nuts against morbidity and mortality from stroke remains somewhat unclear.

Cereals

While a large body of evidence suggests that higher whole-grain intake reduces the risk of type 2 diabetes [145], coronary heart diseases [146] and colon cancer [147], data on the association between whole-grain and/or refined cereal consumption and risk of fatal and non-fatal stroke are not fully consistent.

Whole-grain cereals

Two meta-analyses evaluated the relationship between whole grain cereal intake and risk of fatal and non-fatal stroke. The meta-analysis by Mellen and coworkers, including four prospective studies with 208,143 participants, showed a trend of protection for stroke event rate associated with whole grain cereal intake although results were not significant (OR=0.83, 95% CI 0.68-1.02; Q= 0.04-8.17) [148]. The more recent meta-analysis by Fang et al. included six prospective studies involving 247,487 participants and 1635 stroke events [149]. Pooled results showed a significant reduction of stroke risk by 14% (RR: 0.86; 95% CI 0.73-0.99; I^2=0.0%) in the highest versus the lowest category of whole grain cereal intake.

Refined cereals

The only meta-analysis by Wu and coworkers available on this topic (8 prospective studies with a total of 410,821 subjects and 8284 stroke events) showed no association between refined cereal intake and risk of stroke (SRR:1.02; 95% CI 93-1.10; I^2=0.0%) [150].

Summary of evidence

The most recent meta-analysis of the available prospective studies of whole grain cereal intake and risk of stroke provided evidence of an inverse association, whereas no association was shown for highly refined cereal consumption. The protective effect of whole grain cereals towards stroke may be due to their provision of fiber, vitamins, minerals and other phytochemical compounds, that are removed during the refining process, with some of which having antioxidant properties that may reduce chronic inflammation and blood pressure levels [151].

Olive oil

Olive oil is a main component of the Mediterranean diet and its effect on the risk of stroke has been reviewed by two recent meta-analyses, both dealing not only with stroke but also with ischemic heart disease [113, 152]. The two meta-analyses included the same two cohort studies and consistently reported that an increased consumption of olive oil was associated with a significant reduction in the risk of stroke (respectively, RR: 0.76, 95 % CI: 0.67-0.86; I^2=0.0% for an increment of 25 g/day of olive oil consumption [152] and RR: 0.60; 95% CI: 0.47-0.77; I^2=0.0% in the top compared with the bottom tertile of olive oil consumption [113]).

The meta-analysis by Martínez-González et al. [152] also included the PREDIMED randomized controlled trial [10] that clearly showed a reduction in the risk of stroke after extra-virgin olive oil (EVOO) supplementation. The protective effect of EVOO was attributed to a combined effect of polyphenols, tocopherols and monounsaturated fatty acids.

Summary of evidence

Two meta-analyses and one RCT support the protective effect of EVOO on the risk of stroke.

Chocolate

According to a meta-analysis of five prospective studies with 4,260 stroke cases the risk of stroke is reduced by 19% (RR: 0.81; 95% CI 0.73–0.90 I^2=0.0%) for the highest *vs* the lowest category of chocolate consumption [153].

Late evidence from the EPIC-Norfolk cohort including 20,951 men and women confirmed a beneficial effect of chocolate on the risk of stroke (HR: 0.77; 95% CI 0.62 -0.97) for those in the top quintile of chocolate consumption (16-99 g/day) versus non-consumers of chocolate [154]. Consistently, a meta-analysis of five studies including the aforementioned one, showed that higher compared to lower chocolate consumption was associated with lower stroke risk (RR: 0.79; 95% CI 0.70 -0.87; I^2=0.0%) [154].

Chocolate is an important dietary source of flavonoid antioxidants and its intake resulted in increased high density lipoprotein (HDL), decreased low density lipoprotein (LDL) oxidation, improved endothelial function and reduced blood pressure [155].

Summary of evidence

In conclusion, chocolate consumption is likely to be beneficial for primary prevention of stroke.

Animal sources

Fish

The meta-analysis by Xun et al included 19 independent cohorts from 16 prospective studies for a total of 402,127 individuals and 10,568 incident stroke cases [156]. Compared with those who ate fish never or less than once per month, HRs of incident total stroke were 0.97 (95% CI, 0.87–1.08), 0.86 (0.80–0.93), 0.91 (0.85–0.98; I^2=20.1%) and 0.87 (0.79–0.96) for fish consumption 1–3/month, 1/week, 2–4/week, and >5/week, respectively (P for linear trend=0.09). The association, consistent for fatal and non-fatal stroke, was observed for ischemic stroke, but not for hemorrhagic stroke.

Chowdhury et al. analyzed 21 prospective cohort studies including 675,048 participants and 25,320 incident cerebrovascular events [119]. The RR for stroke, for 2-4 servings versus ≤1 serving a week, was 0.94 (95% CI: 0.90-0.98; I^2=22%) and for ≥5 servings versus one serving a week was 0.88 (0.81-0.96; I^2=20%). In the dose-response analysis (18 studies), an increment of two servings a week of any type of fish was associated with a 4% (95% CI 1%-7 %) reduced risk of cerebrovascular disease. In a subset of studies (62,799 participants) the corresponding RR for white fish types was 1.03 (95% CI 0.90-1.19; I^2=0.0%) and for fatty fish types was 0.84 (95% CI 0.72 to 0.98; I^2=10.1%). The protection was similar for ischemic and hemorrhagic stroke.

The potential benefit of fish consumption could be attributed to the combined and interactive effect of long chain omega 3 fatty acids and to a wide array of nutrients that are abundant in fish (vitamins D and B complex, essential amino acids and trace elements).

Summary of evidence

Consumption of fish is consistently associated with reduced risk of stroke.

Meat and processed meat

Meat consumption is a common source of protein, fat, and energy for humans. However, the 2005 U.S. Dietary Guidelines for Americans recommended that consumption of red and processed meat should be moderated because of the epidemiological evidence that high consumption of meat is associated with increased risk of major chronic degenerative disorders [157]. The meta-analysis by Kaluza et al included six prospective studies with 329,495 participants and 10,630 stroke events [158]. In pooled analysis, each one serving per day of fresh red meat, processed meat, and total red meat was associated with 11%, 13%, and 11% higher risk of total stroke, respectively (fresh red meat: I^2=0%; processed meat: I^2=37.8%; and total red meat: I^2=0%).

Subsequently, Chen et al. published a further meta-analysis of five prospective studies on 239,251 subjects and 9,593 stroke events [159]. In a comparison of the highest against the lowest category of meat intake, the risk of stroke increased by 15% for both red and processed meat intake (I^2=0.0%),

by 9% (I^2=0.0%) for red meat intake and by 14% (I^2=23%)for processed meat intake alone. The association was significant for ischemic stroke, but not for hemorrhagic stroke.

More recently Yang C et al. meta-analyzed seven prospective cohort studies, involving 2,079,236 subjects and 21,730 strokes cases [160]. Total red meat consumption was directly associated with total stroke (RR: 1.14, 95% CI 1.05-1.24; I^2=0.0%), cerebral infarction (RR:1.13, 95% CI 1.0-1.28; I^2=19.8%), and ischemic stroke (RR:1.22, 95% CI 1.01-1.46; I^2=0.0%). A higher risk for total stroke was observed for total red meat consumption above 50 g/day, fresh red meat above 70 g/day, and for any consumption of processed red meat.

A recent observational study in the ARIC population, not included in Yang's meta-analysis, reached similar conclusions [161].

Summary of evidence

There is a strong evidence that the consumption of red and processed meat is associated with an increased risk of ischemic stroke.

The increased risk of stroke associated with higher red meat consumption could be attributed to the combined effect of the high content in saturated fatty acids and cholesterol, to the iron mediated lipid peroxidation and to the high salt content of processed meat.

Milk and dairy products

Two meta-analyses reported data on milk and dairy products and stroke. Hu et al. analyzed 15 prospective cohort studies, with 28,138 stroke events among 764,635 participants [162]. Total dairy (RR: 0.88; 95% CI 0.82-0.94; I^2=61.8%), low fat dairy (RR: 0.91; 95% CI 0.85-0.97; I^2=41.6%), fermented milk (RR: 0.80; 95% CI 0.71-0.89; I^2=0.0%) and cheese (RR: 0.94; 95% CI 0.89-1.00; I^2=0.0%) were all associated with reduced risk of stroke, while whole/high-fat dairy, non-fermented milk, butter and cream were not.

A non-linear relationship was found between milk consumption and risk of stroke, with maximum benefit (18% lower risk) at about 200 ml/day.

Qin et al reviewed 10 studies reporting stroke as outcome and including 504,803 participants with 21,801 stroke cases [163]. They showed that dairy consumption was associated with a significant reduction of stroke rate (RR:0.87; 95%:CI 0.77-0.99; I^2=69.8%); in particular, the associations of low fat dairy and cheese were statistically significant whereas those of high fat dairy, yogurt and butter were not.

Very recently, a further comprehensive systematic review and dose–response meta-analysis of milk and other dairy products in relation to stroke risk has been published, including 18 studies with 762,414 individuals and 29,943 stroke events [164]. A consumption of 200 g of milk daily was associated with a 7% lower risk of stroke (RR: 0.93; 95% CI 0.88–0.98; n=14; I^2=86%). The association was nonlinear, with the strongest beneficial effect at about 125 g/day (RR: 0.86; 95% CI 0.82–0.89; n=13) but benefit remaining significant, although attenuated, up to 750 g/day.

The association between cheese consumption and stroke risk was nonlinear and most pronounced at 25 g/day (RR: 0.91; 95% CI 0.86-0.96; I^2=31.2%). Notably, high-fat milk was associated with an increased stroke risk (RR: 1.04; 95% CI 1.02-1.06; I^2=0.0%), while no associations were found for yogurt, butter, or total dairy.

Possible explanations for the protective effect of reduced fat milk is its content in calcium, magnesium, potassium and bioactive compounds of milk, that have also been associated with a reduced risk of both hypertension and stroke.

Summary of evidence

A regular consumption of milk and dairy products is associated with lower incidence of stroke. The association is more consistent for products with low content in fat.

Eggs

Two meta-analyses explored the possible relationship of egg consumption to stroke risk. While Shin et al. found no association (HR: 0.93; 95% CI 0.81-1.07; I^2=0.0%) [165], the meta-analysis by Rong et al. indicated that an increase of one egg per day was inversely related to hemorrhagic stroke

(RR: 0.75; 95% CI 0.57-0.99; I^2=36.8%) [166]. No association was observed with ischemic stroke (RR: 0.91; 95% CI 0.82-1.02; I^2=0.0%), while the combined relative risk of stroke for an increment of one egg consumed per day was 0.91 (95% CI 0.81-1.02; I^2=0.0%).

Summary of evidence

Egg consumption is poorly associated with stroke risk although a trend toward protection against hemorrhagic stroke was suggested.

2. BEVERAGES

Coffee

In a meta-analysis of six prospective studies, Malerba et al. failed to find any significant relationship between stroke death and consumption of coffee (RR: 0.95; 95 %CI 0.70–1.29; p for heterogeneity=0.009, for highest vs lowest category of coffee intake) while an increment of 1 cup per day was marginally associated with a lower risk of stroke of 5% in men (RR: 0.95; 95%CI 0.89-1.00) [167].

The association between coffee drinking and stroke has been recently addressed by a meta-analysis of 10 prospective observational studies showing reductions in the risk of stroke of 11% (RR: 0.89; 95% CI, 0.84–0.94; I^2=0.0%) and 20% (RR: 0.80; 95% CI, 0.75–0.86; I^2=6.5%) for the consumption of respectively 1.5 cups and 3 cups of coffee a day [168]. At higher intakes (mean of 5.5 cups per day), no protection was detected (RR: 0.95; 95% CI, 0.84–1.07; I^2=54.5%) thus indicating a non-linear association.

Data from a large cohort of over 80,000 Japanese subjects, not included in the aforementioned meta-analyses, showed that, as compared with seldom drinking coffee, the risk of total stroke was lowered by 11% (HR:0.89; 0.80-0.99), 20% (HR:0.80; 0.72-0.90) and 19% (HR:0.81; 0.72-0.91) for individuals drinking coffee 3-6 times/week, 1 cup per day or ≥2 cups of coffee per day, respectively [169]. Risk of cerebral infarction was also reduced at each category of intake (from 1-2

times/week to ≥2 cups per day) whereas a trend for protection was detected for intracerebral hemorrhage (HR: 0.82; 0.66–1.02).

Summary of evidence

Moderate coffee consumption is inversely associated with risk of stroke and is likely to be beneficial for primary prevention. Such evidence is consistent with available data for CVD prevention.

Tea

In a meta-analysis of 14 prospective studies, Shen et al. found that a 3 cups per day higher consumption of tea was associated with 13% (RR: 0.87; 95% CI 0.81-0.94; I^2=53.8%) and 24% (RR: 0.76; 95% CI 0.69-0.84; I^2=0.0%) decreased risk of total stroke and cerebral infarction, respectively, in a dose-response relationship, while associations with cerebral or subarachnoid hemorrhage were not statistically significant [170].

Similar findings were obtained by the meta-analysis of 22 prospective studies by Zhang et al. who found that a difference in tea intake of three cups per day was associated with a reduced risk of total stroke of 18% (RR: 0.82; 95% CI 0.73–0.92; I^2=77.6%), while incidence of cerebral infarction or intracerebral hemorrhage were lowered by 16% (RR, 0.84; 95 % CI 0.72–0.98; I^2=78.7%) and 21% (RR: 0.79; 95 % CI 0.72–0.87; I^2=0.0%), respectively [171].

More recently, the meta-analysis of 9 studies including 259,267 individuals by Pang et al. suggested that individuals consuming 1-3 cups/day of green tea had 36% lower risk of stroke as compared to those with intake <1 cup/day (OR = 0.64, 95% CI 0.47–0.86; I^2=87%) [172].

Summary of evidence

Regular consumption of tea, especially green tea, appears to be beneficial for primary prevention of stroke.

Sweetened beverages

In a dose-response meta-analysis of four prospective studies Xi et al. found that the highest intake of sweetened beverages was marginally associated with an increased risk of total stroke (RR: 1.10, 95% CI 1.00-1.20; I^2=43.4%) as compared with the lowest level [173]. The association was stronger for Caucasian populations (RR: 1.17, 95% CI 1.06- 1.28). No significant association was found in separate analyses on ischemic stroke or hemorrhagic stroke.

Summary of evidence

The only meta-analysis available indicates an increased risk of stroke associated with sweetened beverages intake.

3. ALCOHOL

The association of moderate alcohol consumption with reduced risk of cardiovascular disease has been consistently shown in many epidemiological studies and supported by extensive work; on the other hand, abuse of alcohol is unquestionably harmful [174,175]. Nevertheless, the specific relationship of alcohol consumption with stroke is controversial.

A systematic review and meta-analysis published by Ronksley et al. in 2011 assessed the effect of alcohol consumption on multiple cardiovascular outcomes and concluded that light to moderate daily alcohol intake was associated with a reduced risk of multiple cardiovascular outcomes whereas consumption of larger amounts was associated with higher risks of stroke incidence and mortality [176]. Specifically, those who consumed >60 grams/day were at an increased risk of incident stroke compared with abstainers (RR: 1.62; 95% CI 1.32–1.98).

Zhang et al. have showed evidence of a non-linear relationship between alcohol intake and total stroke risk in an updated meta-analysis based on 20 cohorts from 15 prospective studies [177]. Low alcohol intake (<15 grams/day), compared with no alcohol intake, was associated with a reduced risk of total stroke (RR: 0.85; 95% CI 0.75–0.95; P-value for Q statistic=0.006), but the risk increased with alcohol intakes >30 grams/day (RR: 1.20; 95% CI 1.01–1.43; P-value for Q statistic <0.001). Similar findings were obtained by a dose-response meta-analysis suggesting a potential J-

shaped correlation between alcohol intake and risk of total stroke and stoke mortality (p for non-linearity <0.001, for both dose-response analyses).

Alcohol consumption and ischemic stroke

Comparing to male lifetime abstainers, alcohol consumption of less than 35 g/day was associated with a decreased RR of ischemic-stroke mortality. The risk curve had a nadir (RR: 0.86; 95% CI 0.81-0.93) at 12 grams/day [178]. For women, the lowest risk of ischemic-stroke mortality was detected for those consuming less than 12 grams/day while protective effects were apparent up to 44 grams/day. Likewise, the risk for ischemic-stroke morbidity for both sexes resulted in a J-shaped curve, a protective effect being apparent up to 37 grams/day among men and to 46 grams/day for women. For heavy alcohol intake (12 drinks/day), the relative risks of ischemic-stroke were 1.60 (95% CI 1.38-1.86) for men and 2.15 (95% CI 1.62- 2.86) for women [178].

Evidence of a non-linear relationship between alcohol intake and ischemic stroke risk was shown by Zhang et al. (p < 0.001), confirming that low-alcohol intake (<15 grams/day) was associated with a reduced risk of ischemic stroke (RR: 0.81; 95% CI 0.74–0.90; P-value for Q statistic=0.094), while no significant association was observed with an alcohol intake > 45 grams/day [177].

Alcohol consumption and hemorrhagic stroke

In the meta-analysis by Patra et al., a direct association was observed between alcohol consumption and risk of hemorrhagic stroke (morbidity/mortality), irrespective of sex [178]. While the association was linear for men, the curve for women was J shaped since there was an apparently protective effect of moderate drinking with a nadir being reached at less than 1 drink per day (RR: 0.69; 95% CI 0.54–0.89).

In the dose-response meta-analysis by Zhang et al. a nonlinear relationship between alcohol intake and hemorrhagic stroke risk was found (P = 0.008): while low-to-moderate alcohol intake had no significant effect on the risk of hemorrhagic stroke compared with not drinking alcohol, an alcohol intake of >45 g/day was associated with definitely increased risk [177].

Summary of evidence

The available meta-analyses suggest a J-shaped relationship between alcohol consumption and ischemic stroke, with lower risk for moderate alcohol consumers. In contrast, heavy alcohol consumption increases the risk of both ischemic and hemorrhagic stroke.

Numerous mechanisms have been proposed for the putative protective effect of alcohol towards vascular disease, namely increased levels of high-density lipoprotein cholesterol, decreased levels of low-density lipoprotein cholesterol, reduction in platelet aggregation, beneficial effects on inflammation [175, 179]. Anti-atherogenic and anti-thrombotic effects together with improvement of endothelial function were nevertheless mainly ascribed to non-alcoholic components (polyphenols) of alcoholic beverages [174, 179, and 180]. The blood pressure modulating effect of alcohol [179, 180] could further explain the link between alcohol and stroke.

4. DIETARY PATTERNS

The relationship between different dietary patterns and risk of stroke has been extensively explored. The adherence to a given dietary model is usually assessed by two alternative approaches. The 'a priori-defined' approach is based on predefined diet quality indices using current nutrition knowledge; the 'a posteriori' methodology relies on statistical techniques, and is known as "empirically or data-driven defined dietary patterns" [181].

"A priori"–defined dietary indices

Mediterranean diet

The traditional Mediterranean diet (MD) is intended as the one typically consumed in the early 1950s and 1960s by the populations bordering the Mediterranean Sea. It is essentially characterized by a wide consumption of fruits and vegetables, non-refined grains, nuts, legumes, fish, olive oil as main fat source, moderate wine consumption preferably during main meals and low intake of dairy products and meat [182].

A recent meta-analysis of 12 studies reported an inverse association between degree of adherence to a Mediterranean dietary pattern and risk for stroke (RR: 0.71, 95% CI 0.57-0.89; I^2=69.1%) [183]. The analyses regarding sub-categories of stroke confirmed an inverse relationship with ischemic stroke (RR: 0.52, 95%CI 0.28-0.96; I^2=86.8%) but no significant association with hemorrhagic stroke (RR: 0.97, 95%CI 0.57-1.67; I^2=50%).

The meta-analysis by Kontiogianni et al. [181], updating the previous one [183] by adding 2 cohort studies [184, 185] and the PREDIMED randomized three-arm clinical trial [10], revealed that greater adherence to the MD was associated with 32% lower risk of stroke events (RR:0.68, 95% CI 0.58- 0.79; I^2=0.0%).

Cerebrovascular advantages from the MD were lately established also in a US population setting on 20,197 subjects from the REGARDS study [186]. The authors showed a 21% reduced risk of ischemic stroke for high vs low adherence to the MD (HR: 0.79; 0.65–0.96). No association of adherence to MD with incident hemorrhagic stroke was found.

A more recent meta-analysis of prospective studies and randomized control trials found that individuals in the highest quantile of adherence to the MD had lower incidence of stroke (RR: 0.76; 95%CI 0.60-0.96; I^2=52%) as compared with those least adherent [187].

DASH diet

The Dietary Approaches to Stop Hypertension (DASH) diet was specifically developed to target lowering blood pressure and CVD risk and was included as an example of healthy eating pattern in the 2005 Dietary Guidelines for Americans [188].

Adherence to the DASH diet is appraised by the DASH score that is based on eight criteria: high intake of fruits, vegetables, nuts and legumes, whole grains, low-fat dairy products and low intake of sodium, red and processed meats and sweetened beverages [189].

A meta-analysis of observational prospective studies that examined the DASH-style diet in relation to CVD accrued evidence on the protective role of this dietary pattern against stroke by showing

that imitating a DASH-like diet can significantly reduce the risk of stroke by 19% (RR:0.81; 95%CI 0.72–0.92 for highest vs lowest concordance ntiles; I^2=0.0%) [190].

In a prospective cohort study conducted among 33,671 healthy men and women aged 20–70 years recruited in the Dutch segment of the EPIC study, Struijk et al. found that higher adherence to the DASH diet (expressed as 1 SD increase in the score) was associated with lower risk of fatal/non-fatal stroke (HR:0.90; 95%CI 0.82- 0.99) [191]. No distinction between ischemic and hemorrhagic types was provided.

More recently, Larsson et al sought to test the association between the DASH diet and stroke incidence by using data from two large prospective studies in Sweden for a total sample of 74, 404 men and women (45-83 years of age) [192]. The modified DASH diet score was inversely associated with the risk of ischemic stroke (RR: 0.86; 95%CI 0.78-0.94 for the highest versus the lowest quartile of the score), and showed a trend toward protection against intracerebral hemorrhage (RR: 0.81; 95%CI 0.63-1.05) or subarachnoid hemorrhage. By using the DASH target intakes for nine nutrients (total fat, saturated fat, protein, fiber, cholesterol, calcium, magnesium, potassium and sodium), Chan et al. highlighted only a trend towards an inverse association between the DASH diet and risk of stroke in men (HR:0.62; 95%CI 0.38-1.04) [185].

Other a priori-defined dietary patterns

The Healthy Eating Index (HEI) is a summary measure of the degree to which an individual's diet is aligned with Dietary Guidelines for Americans, 2005 [189]: in the EPICOR study it was associated with lower risk of ischemic stroke (HR: 0.54; 95%CI 0.31–0.94) [193].

The healthy Nordic food index includes foods that originate in Scandinavia, are commonly consumed in Nordic countries, and are likely to have beneficial health effects. This resulted in inclusion of six food groups: rye bread, oatmeal, apples/pears, cabbages, root vegetables and fish/shellfish [194]. On the wake of previous documented beneficial effects of the Nordic dietary

pattern on short-term markers of CVD, Roswall et al. in the Swedish Women's Lifestyle and Health cohort failed to find any association with risk the of stroke (HR:0.99; 95%CI 0.94–1.04) [194].

The Recommended Food Score (RFS) tries to define the overall diet quality by discriminating "healthy" from "less healthy" foods based on dietary guidelines and present knowledge [195]. In the Swedish Mammography Cohort, a higher RFS was associated with a 15% reduced risk of total stroke (RR: 0.85; 95%CI 0.76–0.95) [195]. The risk of cerebral infarction was also reduced by 13% (RR: 0.87; 95%CI 0.76–0.99) with a non-significant similarly downward trend for hemorrhagic stroke (RR: 0.77; 95%CI 0.58–1.01).

Empirically derived dietary patterns

As for the 'a priori' defined diets, the association of 'a posteriori'-identified dietary patterns has been widely assessed and has produced contrasting findings.

A recent meta-analysis by Zhang et al. including a total of 21 studies, in which dietary patterns were identified by factor analysis or principal component analysis, showed lower risk of stroke for the highest compared with the lowest categories of the "healthy" dietary pattern, which was characterized by high intakes of vegetables, fruits, fish, low-fat milk, and whole grains (OR: 0.77; 95%CI 0.64-0.93; I^2=87%) [196].

A meta-analysis by Rodriguez-Monforte et al. estimating the association between empirically derived dietary patterns and CVD, by using data from eight cohort studies, revealed a non-significant trend towards an inverse association between prudent/healthy dietary patterns and risk of stroke (RR: 0.86; 95% CI 0.74- 1.01; I^2=59.5%) (197].

Western dietary patterns

Two recent meta-analyses failed to find any significant association between adherence to a Western-type diet (rich in i.e. red and/or processed meats, refined grains, sweets) and risk of stroke [196, 197].

Summary of evidence

A persuasive body of evidence supports a favorable role of dietary models characterized by a relatively high consumption of plant foods (fruits, vegetables, unrefined cereals, legumes, nuts), use of extra virgin olive oil as main source of fat, moderate consumption of fish, milk and dairy products, and a lower consumption of meat (particularly of red and processed meats) along with regular consumption of low-to moderate amounts of red wine at the main meals.

DISCUSSION

This document reviews the available evidence from both observational and interventional studies concerning the association between nutritional habits and risk of stroke and provides evidence-based recommendations for dietary modifications amenable to reduce stroke morbidity and mortality rates. A major strength of the present document is the performance of a systematic review of the available literature and the adoption of a rigorous methodology for the assessment of the value of the evidence provided by each study and by the meta-analyses thereof, based on the widely recognized SIGN system. As pointed out [198], a properly conducted systematic review is an efficient way to summarize the best available research evidence for a focused research question. Overall, the available literature provides convincing evidence that diet quality affects the risk of stroke to a significant extent. This may be stated for many selected nutrients and foods based on the results of good quality meta-analyses and of studies on animal models which add biological plausibility to the epidemiological data mainly deriving from observational studies.

The main limitation is given by the substantial lack of randomized controlled intervention trials specifically designed to test the effect of a given dietary modification on stroke as the primary outcome. Unfortunately, randomized controlled trials are expensive, may pose ethical problems and are difficult to perform because of the need to monitor a large study population over a long follow-up period if the long-term effect of intervention on hard health outcomes is to be assessed.

Other limitations are given by the possibility of residual confounding affecting many observational studies and by the limited amount of stroke-specific research studies.

Moreover, a common limitation of the studies exploring the role of diet in relation to stroke is the inadequate discrimination between ischemic and hemorrhagic type of stroke, actually mainly due to the relatively low incidence of the latter. In fact, very few studies reached significant results about the possible association between dietary habits and risk of hemorrhagic stroke. Indeed, the different physiopathological background of the two types of stroke would require a separate evaluation especially when dealing with potential factors of risk/protection.

Overall, we found a consistent body of evidence for some nutrients and food groups but not for others. Examples are given by the convincing evidence of the protective role of adequate dietary calcium or nut intake which translated in a strong recommendation in favor, whereas no such evidence was available in either direction for egg consumption for which accordingly no recommendation was provided. In some cases, additional studies are obviously needed in order to clarify their potential contribution to stroke prevention. As an example, little is known on the role of sweetened beverages or of some specific foods such as eggs in modulating the risk of stroke. In addition, a major research need emerged from this consensus is a better understanding of the possible role of non-nutritional components carried by some foods, including their content in pesticides, nitrites or heavy metals, which may yield undesirable health outcomes on a longer-term basis [199].

A last positive consideration is that the evidence available with regard to the influence of dietary patterns appears to be in general more solid than the one available for single nutrients or foods also thanks to the support provided by a few randomized controlled trials.

Yet, the SINU Nutrition and Stroke Working Group recommendations conform to the concept that people eat a complex and variable admixture of foods, not just nutrients, and that, as a consequence, dietary patterns provide a better picture of food and nutrient consumption and may thus be more predictive of disease risk as compared with intake of individual foods or nutrients. Addressing dietary patterns allows to account for the complexity of overall diet and the potential interactions between nutrients and food groups [200, 201], thus facilitating public guidance and minimizing

industry manipulation [181].

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Appendix 1

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Table 1. Example of the search strategy model adopted for sodium.

(("sodium, dietary"[MeSH Terms] OR ("sodium"[All Fields] AND "dietary"[All Fields]) OR "dietary sodium"[All Fields] OR ("dietary"[All Fields] AND "sodium"[All Fields]) OR "dietary sodium"[All Fields] OR "sodium chloride, dietary"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields] AND "dietary"[All Fields]) OR "dietary sodium chloride"[All Fields] OR ("dietary"[All Fields] AND "sodium"[All Fields])) OR (("sodium, dietary"[MeSH Terms] OR ("sodium"[All Fields] AND "dietary"[All Fields]) OR "dietary sodium"[All Fields] OR "sodium"[All Fields] OR "sodium"[MeSH Terms]) AND intake[All Fields]) OR ("sodium chloride, dietary"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields] AND "dietary"[All Fields]) OR "dietary sodium chloride"[All Fields] OR ("dietary"[All Fields] AND "salt"[All Fields]) OR "dietary salt"[All Fields]) OR (("sodium chloride"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields]) OR "sodium chloride"[All Fields] OR "salt"[All Fields]) AND intake[All Fields])) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields]).

Table 2. Revised grading system for recommendations in evidence based guidelines.

Levels of evidence

- *1++* High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
- *1+* Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
- *1−* Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias.
- *2++* High quality systematic reviews of case-control or cohort studies *or* high quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.
- *2+* Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
- *2−* Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal.
- *3* Non-analytic studies, e.g. case reports, case series.
- *4* Expert opinion.

Grades of recommendation *

Undesirable consequences clearly outweigh desirable consequences	***Strong recommendation against***
Undesirable consequences probably outweigh desirable consequences	***Conditional recommendation against***
Balance between desirable and undesirable consequences is closely balanced or uncertain.	***Recommendation for research and possibly conditional recommendation for use restricted to trials***
Desirable consequences probably outweigh undesirable consequences	***Conditional recommendation for***
Desirable consequences clearly outweigh undesirable consequences	***Strong recommendation for***

*From ref. 16

Table 3 Syntheses and recommendations for micronutrients, macronutrients, food groups and dietary patterns

Dietary component	Synthesis	Potential mechanisms	Recommendation	Level of evidence	Strength of recommendation
Micronutrients					
Electrolytes					
Dietary calcium	Higher dairy calcium intake is associated with lower stroke risk. Higher total calcium intake is beneficial in populations with a relatively low average calcium intake.	Possible beneficial effects of low-fat dairy products on blood pressure and systemic inflammation, particularly in overweight individuals	An adequate dietary calcium intake is recommended according to age. This may be attained in the context of a balanced diet through lower fat milk and dairy products, vegetables, legumes and calcium-rich drinking water.	2++	Strong recommendation in favor
Calcium supplement	Calcium supplements may increase the risk of myocardial infarction and stroke.		Extreme caution should be used in the prescription of calcium supplements, unless needed to correct proven deficits.	1+	Strong recommendation against
Magnesium	Inverse association between dietary magnesium intake and ischemic stroke risk.	Beneficial effects on blood pressure, insulin resistance, and blood lipids.	An adequate dietary magnesium intake is recommended according to age.	2++	Strong recommendation in favor
Potassium	Evidence of an inverse association between potassium intake and risk of stroke. The association is likely to be more favorable for ischemic rather than for hemorrhagic stroke.	Blood pressure lowering effect.	Dietary potassium intake should be increased possibly to 100 mmol (3.9 g)/ day	2++	Strong recommendation in favor
Sodium	There is solid evidence on the association of higher salt intake and risk of stroke.	Strong relationship between salt intake and blood pressure.	Sodium (salt) intake should be reduced to or below 2 g/day (5 g of salt)	2++	Strong recommendation against

Vitamins and antioxidants					
Folates	Adequate dietary folate intake has been associated with lower risk of stroke, in particular of the ischemic type.	The beneficial effect is likely to be independent from homocysteine.	Regular consumption of high folate-containing foods should be promoted.	2++	Strong recommendation in favor
Vitamin B_6, Vitamin B_{12}	The association between dietary or plasma levels of Vitamin B_6/ Vitamin B_{12} with stroke risk is uncertain.			2+	Strong recommendation against
Vitamin A, Vitamin E	No association between vit. A intake and stroke risk. Both higher dietary and supplemented vitamin E intakes are associated with increased risk of hemorrhagic stroke.		The use of antioxidant vitamin supplements for the prevention of stroke is not indicated.	2+	Strong recommendation against
Vitamin C	Both higher dietary and blood levels of vitamin C have been associated with reduced risk of stroke.	Prevention of endothelial dysfunction, anti-inflammatory and anti-hypertensive role.	An adequate dietary intake of vitamin C is recommended.	2+	Strong recommendation in favor
Folates, Vitamin B_6, Vitamin B_{12} supplements	No support for the use of ~~antioxidant~~ vitamin supplements in the prevention of stroke.		Vitamin B_6/ Vitamin B_{12}/folate supplements are not beneficial for the prevention of stroke.	1+	Strong recommendation against
Vitamin D	Low blood levels of vitamin D are associated with increased stroke incidence.	Favorable role on blood pressure, insulin sensitivity, renin-angiotensin system, endothelial function, proliferation of vascular smooth muscle cells,	Vitamin D deficiency, as indicated by a plasma concentration of 25-hydroxycholecalciferol below 50 nmol/L (20 ng/mL) must be corrected appropriately.	2++	Strong recommendation in favor

		regulation of parathyroid hormone levels.			
Dietary fiber	Dietary fiber intake is associated with reduced risk of stroke: effect more pronounced for ischemic stroke and for women.	Reduction of blood pressure levels, improvement of insulin resistance, lipid profile fibrinolysis, inflammation and endothelial function.	Dietary fiber intake should be increased to 25 g/day by consumption of adequate amounts of plant foods.	2++	Strong recommendation in favor
Macronutrients					
Carbohydrates					
Carbohydrate, GI and GL	A high dietary GL is associated with the risk of stroke while total CHO intake and GI are not	Vascular injury induced by a chronic increase in blood glucose and postprandial insulinemia, which act through both oxidative stress and a sub-clinical systemic inflammation with production of oxidized lipoproteins and AGEs.	A low-glycemic load diet is recommended.	2++	See related food (i.e. Cereals or Sweetened beverages)
Dietary MUFA	No relationship between dietary MUFA and risk of stroke.		The intake of MUFA-rich foods should be encouraged	2++	See related food (vegetable sources: i.e. olive oil, nuts; animal sources: i.e. lard, meat)
Dietary SFA	No association was found between dietary SFAs intake and stroke. Reduction or substitution of SFAs with PUFAs or MUFAs is not associated with stroke risk.		The intake of SFA-rich foods should be limited according to specific guideline recommendations.	2++	See related food (i.e. butter, dairy products, meat, seasoned cheese).
Dietary TFA	No association between TFA intake and risk of stroke.		The intake of foods rich in TFA should be limited according to specific guideline recommendations.	2+	See related food (i.e. margarine, butter).
Dietary PUFAs	No association between		The intake of foods rich in	2++	See related food (i.e.

	omega-3 long chain fatty acids or α-linolenic acid with either ischemic or hemorrhagic stroke.		PUFA should be encouraged according to specific guideline recommendations.		vegetable oils, nuts, fish).
PUFA supplements	Evidence from intervention studies of primary and secondary prevention of stroke failed to find any association between omega-3 fatty acid supplementation and either ischemic or hemorrhagic stroke.		Use of fat supplementation should be avoided.	1+	Strong recommendation against
Protein	No sufficient evidence in support of any association between dietary protein intake and stroke.		It is suggested to refer to guideline specific recommendations on foods containing either vegetable or animal proteins.	2++	See related food (animal sources: i.e. meat, fish, eggs, seasoned cheese; vegetable sources: i.e. legumes, nuts)
Food groups					
Vegetables sources					
Fruits and vegetables	Solid evidence of a dose-dependent inverse association between higher fruit and vegetables intake and reduced risk of total, ischemic and hemorrhagic stroke.	Reduction of blood pressure and improvement of microvascular function.	Fruit and vegetable intake should be increased to 5 servings a day to ensure adequate intakes of dietary fibers, minerals (potassium, magnesium), vitamins (e.g. folic acid) and other nutrients.	2++	Strong recommendation in favor
Legumes	No association between legumes intake and stroke risk.		Dietary intake of legumes is recommended in line with beneficial effects documented for cardiovascular health.	2++	
Nuts	Evidence of beneficial effect of nut intake against stroke risk.	Improvement of markers of oxidation, inflammation and endothelial function.	Regular nut intake should be encouraged (20-30 g/die) In the framework of a well-	1-	Strong recommendation in favor

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			balanced diet in view of their well-documented cardiovascular health benefits		
Whole-grain Cereals	Limited evidence for a reduced risk of stroke at higher intakes.	Improvement of blood pressure, body weight, insulin –resistance, lipid profile and subclinical inflammation.	Dietary intake of whole-grain cereals should be recommended in line with documented cardiovascular advantages.	2+	
Olive oil	Evidence of a reduced risk of stroke for higher intakes of extra virgin olive oil.	Combined effect of polyphenols, tocopherols and monounsaturated fatty acids.	Extra virgin olive oil (EVOO) is indicated as main dietary fat source.	1+	Strong recommendation in favor
Chocolate	Moderate intake of dark chocolate is associated with reduced risk of total stroke.	Increased high-density lipoprotein (HDL), decreased low-density lipoprotein (LDL) oxidation, improved endothelial function and reduced blood pressure.	Regular and moderate consumption of dark chocolate should be encouraged, also in light of its documented cardiovascular health advantages.	2++	Strong recommendation in favor
Animal sources					
Fish	Reduced risk of total and ischemic stroke with higher fish consumption. No consistent association with hemorrhagic stroke.	PUFA, vitamin D and B, potassium, calcium and magnesium contained in fish may have favorable vascular effects.	Fat or semi-fat fish intake is recommended at least twice a week also in light of its largely documented cardiovascular health advantages.	2++	Strong recommendation in favor
Meat and processed meat	High intake of meat and processed meat is associated with a higher risk of total and ischemic stroke.	Likely linked to the unfavorable effects of SFA content, high heme, lipid peroxidation, and high salt content of processed meat on blood pressure.	Dietary intake of meat should be limited to 1-2 times a week; however, consumption of processed meat should be only occasional.	2++	Strong recommendation against
Milk and dairy products	Lower risk of ischemic and	Possibly mediated by high	Regular consumption of low	2++	Strong recommendation

	hemorrhagic stroke observed with regular moderate consumption of low-fat milk and dairy products.	content of calcium, magnesium, potassium and bioactive peptides.	fat milk and dairy products is recommended.		in favor
Eggs	No association with either ischemic or hemorrhagic stroke was documented.		No recommendation can be provided	2++	
Beverages					
Coffee	Regular coffee intake is associated with lower risk of total and ischemic stroke.	Polyphenols, chlorogenic acid, caffeine, niacine and lignans.	Moderate coffee consumption is recommended.	2++	Strong recommendation in favor
Tea	Higher tea consumption is associated with reduced risk of total, ischemic and hemorrhagic strokes.	Favorable health effects of antioxidants, catechins e theanine.	Moderate consumption of tea (and particularly green tea) is recommended.	2++	Strong recommendation in favor
Sweetened beverages	Consumption of sweetened beverages is associated with Increased risk of total and ischemic stroke	Unfavorable effect on LDL-cholesterol, VLDL, blood glucose and insulin.	The consumption of sweetened beverages should be discouraged.	2++	Strong recommendation against
Alcohol	Evidence of a J-shaped relationship between ethanol intake and stroke risk. Alcohol abuse is associated with increased risk of total, ischemic and hemorrhagic stroke.	Moderate consumption is associated with Improved lipid profile, reduction in platelet aggregation, beneficial effects on inflammation, antiatherogenic and anti-thrombotic effects and regulation of endothelial function and blood pressure.	Alcohol intake should be limited to 1 drink per day for women and to 2 drinks per day for men.	2++	Strong recommendation in favor of moderate and regular intake. Strong recommendation against alcohol intake above moderate amounts.
Dietary patterns					
Mediterranean-type	A Mediterranean dietary pattern is associated with	Possibly related to anti-inflammatory, antioxidant,	A Mediterranean-type of diet, rich in fruits, nuts, vegetables,	1+	Strong recommendation in favor

	lower morbidity and mortality from stroke.	anti-atherogenic and antithrombotic action of main components of the Mediterranean diet.	non-refined grains, fish, extra virgin olive oil as main fat source, moderate intakes of low-fat milk and dairy products but low in meat and processed meat, and moderate intake of alcohol during main meals, is highly recommended.		
DASH diet	A DASH dietary pattern is associated with reduced risk of stroke.	Possibly related to large amount of plant foods and dairy products and to low salt intake.	A DASH dietary pattern can be recommended.	2++	Strong recommendation in favor
Other healthy dietary patterns	Favorable association between stroke risk and other healthy dietary patterns.	Possibly related to large amounts of vegetable dietary sources.	Other healthy dietary patterns, mainly based on large amounts of plant foods, are acceptable.	2++	
Western dietary patterns	No consistent evidence available on the association between Western-type diets and risk of stroke.		A Western dietary pattern should be discouraged because of its well-documented adverse effects on CVD health and risk factors.	2++	Strong recommendation against

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Highlights

- Systematic review of nutrition-related risk factors for primary prevention of stroke
- Evidence organized into three individual areas to provide a user-friendly overview
- Quality of evidence and strengths of the recommendations by validated tools
- 36 Syntheses and 36 Recommendations were eventually prepared