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META-ANALYSIS

Adherence to the Mediterranean diet and risk of stroke and stroke subtypes

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Abstract
Several meta-analyses including a small number of cohorts showed inverse associations between the Mediterranean Diet (MedDiet) and risk of stroke. However, it remains unclear whether such a relation varies by region of the study population or by major subtypes of stroke. We searched PubMed and EMBASE databases for relevant studies and we further included unpublished results from the Singapore Chinese Health Study ($N=57{,}078$) and the Seguimiento Universidad de Navarra (SUN) study ($N=12{,}670$). We used a random-effects model to calculate summary relative risk (RR) with 95% confidence intervals (CI) of stroke for each 4-point increment of the MedDiet score, roughly corresponding to the difference between extreme quintiles of the MedDiet score among participants of the included studies. The final analyses included 20 prospective cohort studies involving 682,149 participants and 16,739 stroke cases. The summary RRs for each 4-point increment of the MedDiet score were 0.84 (95% CI 0.81–0.88; $I^2=11.5\%$) for all combined, 0.76 (95% CI 0.65–0.89) for studies in Mediterranean populations and 0.86 (95% CI 0.83–0.89) for those in non-Mediterranean populations. Lower risk of stroke associated with higher MedDiet score also was observed in the analyses stratified by study population and methodological characteristics including study risk of bias, version of the MedDiet index, and definition of moderate alcohol consumption. The MedDiet was similarly associated with lower risk of ischemic stroke (RR 0.86, 95% CI 0.81–0.91; nine studies) and hemorrhagic stroke (RR 0.83, 95% CI 0.74–0.93; eight studies). Our meta-analysis suggests that adhering to the Mediterranean diet was associated with lower risk of stroke in both Mediterranean and non-Mediterranean populations, and for both ischemic stroke and hemorrhagic stroke risk.

Keywords Mediterranean diet · Ischemic stroke · Hemorrhagic stroke · Cohort studies · Meta-analysis

Introduction

Stroke is the second leading cause of mortality and the third cause of disability worldwide, imposing serious threats on public health [1]. It has been estimated that in 2013, there were 10.3 million new-onset cases of stroke and 6.5 million deaths from stroke [2]. Despite declines in worldwide age-standardized mortality rate, the absolute numbers of both incident stroke and stroke deaths have been increasing in the past decades, and the increases will continue globally but particularly in low-income and middle-income countries as a consequence of the ongoing population growth, ageing, and epidemiological transitions [3, 4]. Stroke appears to be a largely preventable condition. According to evidence from several large-scale international studies [4, 5], approximately 90% of the stroke burden may be attributable to modifiable risk factors including a poor diet, which highlights the potential of primary prevention. With regard to dietary factors, the Global Burden of Disease Study 2013 [4] ranked a low-fruit diet, a high-sodium diet, and a low-vegetable diet as the second, fourth and sixth leading modifiable contributors to stroke burden. A national analysis of the US population also

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suggested that more than half of stroke deaths in 2012 could be attributed to suboptimal diets [6].

The Mediterranean diet (MedDiet), an eating pattern found among populations living in the Mediterranean Basin during the 50 s and 60 s of the twentieth century, has been extensively studied and related to multiple health outcomes [7–9]. A large body of evidence is available and it is recently growing to support that this diet may be particularly beneficial for stroke prevention. In a landmark trial of high-risk population in Spain, a 5-year intervention with a MedDiet significantly reduced the incidence of major cardiovascular disease (CVD), predominantly stroke: The recently republished results of this trial including many new thorough analyses and addressing potential criticisms supported this strong protective effect [10]. Results from observational cohort studies also supported that greater adherence to the MedDiet is associated with a lower risk of stroke [11–13]. However, questions remain as to whether the MedDiet can similarly confer benefits for Mediterranean and non-Mediterranean populations and for the prevention of ischemic and hemorrhagic stroke, two major subtypes of stroke. It is also uncertain how variations in the components of the MedDiet indices used in different studies may influence this association. A clearer understanding of these questions is relevant for informing stroke prevention strategies. Therefore, we performed a meta-analysis to evaluate the association between the MedDiet and risk of stroke and stroke subtypes, including both published and unpublished results from a large number of prospective studies conducted in different world regions.

Methods

Literature search

We planned, conducted, and reported this study in adherence to the guidelines of the 'Meta-analysis Of Observational Studies in Epidemiology group' [14]. We performed a literature search on PubMed and EMBASE databases through February 10, 2019 using the search strategy reported in the Supplemental Methods, without restrictions on language or publication type. The reference lists of retrieved full publications and previous systematic reviews and meta-analyses [9, 11–13] were hand screened to identify any additional studies. We also reviewed the commentary and responding letters attached with the full publications for additional information. Two authors (GCC and NN) independently accessed the eligibility of the identified records, with any disagreements resolved by group discussions. We further contacted the corresponding authors to obtain additional unpublished data wherever necessary.

In addition to published studies, we assessed the MedDiet in relation to mortality risk due to total stroke, ischemic/unspecified stroke, and hemorrhagic stroke in the Singapore Chinese Health Study (SCHS) [15]. Although some of the stroke cases in the SCHS were unspecified, our previous validation study showed that most of these cases were ischemic [16]. We also investigated the relationship between the MedDiet and risk of total stroke (fatal/non-fatal) in the Seguimiento Universidad de Navarra (SUN) (University of Navarra follow-up) study [17]. Thereafter, we included these unpublished results in the meta-analysis. More detailed procedures for the analyses of both cohorts are available in the Supplemental Methods.

Study selection

To be included, published studies had to meet the following criteria: (1) the study design was prospective; (2) the exposure of interest was the MedDiet adherence as reflected by a specific dietary index, for example the commonly used MedDiet index developed by Trichopoulou et al. [18] or by Fung et al. [19]; (3) the outcome of interest was stroke, including any fatal/non-fatal ischemic stroke, hemorrhagic stroke, or other cerebrovascular accidents; and 4) risk estimates such as relative risk (RR) or hazard ratios (HR) with corresponding 95% confidence interval (CI) of stroke were available. We excluded studies in which all participants were patients with major CVD at baseline; however, we included studies that enrolled participants with CVD risk factors (e.g. diabetes) [20, 21]. For two publications [22, 23] that used the same study population, we included the one [22] with larger number of cases and used results for stroke mortality that were only available in the other [23] for subgroup analyses.

Data extraction and quality assessment

Using a standardized data-collection form, we collected the following data from each included study: the first author's last name, publication year, country, study name, years of follow-up, age, sex, number of participants and stroke cases, patients excluded at baseline, method for dietary assessment, components of the MedDiet, definition for moderate drinking, the maximally adjusted risk estimates with 95% CIs for each category of the MedDiet score and/or for per-unit increment of the score, and the statistical adjustments made. We evaluated risk of bias for each study using the ROBINS-I (Risk Of Bias In Non-randomized Studies-of Interventions) tool [24]. The tool consisted of seven domains: confounding, selection of participants, exposure measurement, misclassification of exposure during follow-up, missing data, outcome measurement, and selective reporting. Bias specific to this meta-analysis included using a dietary index that may not reflect the MedDiet well.

Statistical analysis

Risk estimates of stroke in the primary studies were reported based on distinct comparisons of the MedDiet score (e.g. for extreme quintiles/quartiles/tertiles or per unit increment). For consistency, we estimated for each study the RR with 95% CI for a 4-point increment of the MedDiet score. Such an increment approximates difference between extreme quintiles of the MedDiet score in included studies, because the range between the medians of the extreme quintiles of the score was around 4 points across studies of divergent regions (e.g. the SCHS, the SUN study, and several other studies of the Mediterranean [25] and non-Mediterranean countries [19, 20, 26]). For studies where the MedDiet score was reported as a continuous variable (e.g. per 1-point or SD increment), the results were converted to the estimates for a 4-point increment of the score. For studies that reported the MedDiet score only as a categorical variable, we calculated the dose–response estimates for a 4-point increment by use of the method proposed by Greenland and Longnecker [27] and Orsini et al. [28]. The reference group of one study [26] was not the lowest category of the MedDiet score and there was no response after author correspondence; therefore, we set the lowest category as the new reference category for this study and calculated new risk estimates according to the method of Hamling et al. [29].

Several studies [23, 30, 31] used two or more versions of the MedDiet indices, and we included the results based on the index developed by Trichopoulou et al. or by Fung et al. for the sake of improving consistency with most other studies included. For studies [32–35] that reported only sex- or stroke subtype-specific results without presenting overall estimates, the results were pooled with a fixed-effect model and the combined estimates were used in the main analyses. Several studies used modified MedDiet indices and the possible range of these scores were 0–7 [36], 0–8 [34, 37], 0–14 [21], 0–18 [38], rather than 0–9. For these studies, the reported results were standardized to the risk estimates corresponding to a 9-point scale of the MedDiet score. For example, the log-scale RR with corresponding variance (for 4-point increment) in the 14-point scale each was multiplied by 1.56 (14/9) to derive the log-scale RR and variance (for 4-point increment) in the 9-point scale. Afterward, we combined study-specific estimates using a random-effects model [39], which considers both within- and between-study variation.

We examined potential non-linear relationship between the MedDiet score and stroke risk, with the score being modeled using restricted cubic splines with three knots at percentiles 10%, 50% and 90% of the distribution [40]. A *P* value for non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero. We also performed stratified and meta-regression analyses according to the following study and population characteristics: age and sex of participants, duration of follow-up, number of cases, outcome of stroke (fatal and/or non-fatal), stroke subtype (ischemic and hemorrhagic), study risk of bias assessed by the ROBINS-I, study region, version of the MedDiet score, definition for moderate alcohol drinking, whether patients with other major CVD at baseline were excluded, and whether the analyses were adjusted for potential mediators such as blood pressure and lipids. We further conducted sensitivity analyses to evaluate the robustness of the summary results (e.g. removing studies that included high-risk population and performing meta-analysis that compared highest with the lowest categories of the MedDiet score).

Heterogeneity among studies was assessed using the Q and I^2 statistics [41]. For the Q statistic, $P<0.1$ was considered as statistically significant, and for the I^2 statistic, a value of < 30%, 30–75%, and > 75% was deemed as little or no, moderate, and high heterogeneity. Potential publication bias was evaluated using Egger's linear regression test, Begg's rank correlation test and funnel plots [42, 43]. All statistical analyses were performed using STATA version 12.0 (STATA Corp., College Station, TX, USA).

Results

Literature selection

A flow chart of the study selection is reported in Fig. 1. Briefly, a total of 839 unique reports were identified after removing duplicates, of which 45 were retrieved for more detailed review. Two additional reports were found by screening the references of relevant manuscripts. Twenty-nine reports were excluded after additional evaluations (Supplemental Table 1), resulting in 18 published eligible studies [19–22, 25, 26, 30–38, 44–46], of which 16 were reported as full articles and two [20, 46] as conference abstracts. After the addition of unpublished data from the SCHS and the SUN cohorts, our final analysis included 20 prospective cohort studies. Among these studies, results for ischemic and hemorrhagic stroke were separately reported for eight studies [19, 30, 33–35, 45, 46] (including the SCHS) and results for ischemic stroke were acquired through author correspondence for one additional study [38].

Study characteristics

The characteristics of the included studies are summarized in Table 1. Overall, the 20 studies included 682,149 participants and 16,739 stroke cases. For the two unpublished studies (the SCHS and the SUN), baseline population characteristics according to quintiles of the MedDiet score are

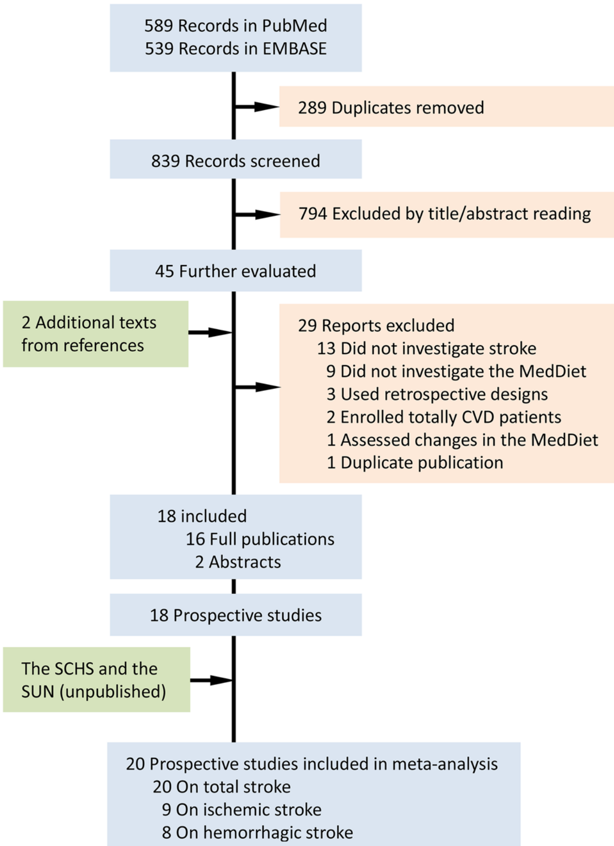

Fig. 1 Literature selection for the meta-analysis. SCHS, Singapore Chinese Health Study; SUN, Seguimiento Universidad de Navarra (University of Navarra follow-up)

reported in Supplemental Tables 2 and 3. After the adjustment for multiple potential confounders, a higher MedDiet score was significantly associated with a lower risk of stroke mortality in the SCHS (Supplemental Table 4) and non-significantly with a lower risk of stroke in the SUN study (Supplemental Table 5).

Of the 20 included studies, six were from the US, two from Eastern Asia, five from Mediterranean countries (Italy, Greece and Spain), six from non-Mediterranean European countries, in addition to one from five Mediterranean and non-Mediterranean European countries. Duration of follow up and sample size ranged substantially across studies. Three studies included women only, whereas all other studies included both men and women. Participants in three studies [20, 21, 36] were high-risk individuals who had diabetes [20] or multiple other CVD risk factors [21, 37]. The outcome was fatal and non-fatal stroke in all except for three studies for which only fatal stroke were evaluated. All studies included alcohol consumption as a MedDiet component with different definitions of moderate consumption. Other potentially beneficial and detrimental components of the MedDiet used in each study are presented in Supplemental Tables 6 and 7. Reported results and statistical adjustments used in each study are summarized in Supplemental Table 8. For the outcomes of total stroke, ischemic stroke and hemorrhagic stroke, the proportion of studies without serious risk of bias was 70% (14/20), 67% (6/9) and 100% (6/6), respectively (Supplemental Table 9).

MedDiet and risk of stroke and stroke subtypes

A meta-analysis of the 20 prospective studies showed a significant 16% (RR 0.84, 95% CI 0.81–0.88) lower risk of stroke for each 4-point increment in the MedDiet score, with limited evidence for heterogeneity ($P=0.31$; $I^2=11.5\%$) (Fig. 2). The association appeared stronger for the studies of the Mediterranean populations (RR 0.76, 95% CI 0.65–0.89) than for other studies (RR 0.86, 95% CI 0.82–0.89), but this difference was not significant ($P_{\text{difference}}=0.17$). There was no evidence for a nonlinear relationship between the MedDiet score and risk of stroke ($P_{\text{nonlinearity}}=0.15$, Supplemental Figure 1).

As to stroke subtypes, results of meta-analysis showed that each 4-point increment of the MedDiet score was significantly associated with 14% (95% CI 9–19%; $I^2=0\%$; nine studies with 6630 cases and 379,477 participants) lower risk of ischemic stroke and 17% (95% CI 7–26%; $I^2=0\%$; eight studies with 2027 cases and 356,200 participants) lower risk of hemorrhagic stroke (Fig. 3).

Stratified and sensitivity analyses

The observed inverse association between the MedDiet score and risk of stroke was consistent across various predefined subgroup populations, although the pooled effect estimates were not always comparable within these strata (Table 2). The association for total stroke was stronger for studies with potentially serious risk of bias than those without ($P_{\text{difference}}=0.005$); nevertheless, most (90%) stroke cases were included in the studies without serious risk of bias, and the risk estimate based on the latter was comparable with the overall summary estimate. The association did not vary by the definition of moderate alcohol drinking, and the MedDiet indices based on Trichopoulou et al. and Fung et al. were similarly associated with lower risk of stroke. Results for fatal stroke were reported for seven studies (including the SCHS) and acquired through author correspondence for one additional study [25]. A meta-analysis of these eight studies (6114 stroke deaths) showed a significant 16% (95% CI 8–20%) lower risk of stroke mortality for each 4-point increment of the MedDiet score (Table 2).

The summary RR was 0.84 (95% CI 0.79–0.88) when restricting the analysis to the 16 published full reports. Results were similar after excluding three studies [35, 36, 45] in which a small proportion of cases were patients with

Table 1 Characteristics of the 20 prospective studies examining relationship between the Mediterranean diet and risk of stroke

Author (year) (Country)	Study, follow-up duration	Participants	Mean age	Excluded patients at baseline	No. of components[a]	Moderate drinking definition	Diet assessment	Outcomes
Fung (2009) (US)	NHS, 18.7 yr	74,886 W	NR (38–63 yr)	CHD, stroke, and diabetes	9	5–15 g/d	FFQ (repeated)	1480 nonfatal and 283 fatal stroke (959 IS, 329 HS, and 475 unclear subtype)
Gardener (2011) (US)	NOMAS, 9.0 yr	2568 M&W	69 yr	MI and stroke	9	> 0 to ≤ 2 drinks/d	FFQ	197 fatal/nonfatal stroke (171 IS and 26 HS)
Agnoli (2011) (Italy)	EPIC-Italy, 7.9 yr	40,681 M&W	49.8 yr	MI, stroke, diabetes, hypertension, and dyslipidemia	9	10–50 g/d for M, 5–25 g/d for W	FFQ	178 fatal/nonfatal stroke (100 IS and 47 HS)
Hoevenaar-Blom (2012) (the Netherlands)	EPIC-NL, 11.8 yr	34,708 M&W	43 yr for M and 52 yr for W	CVD and T2D	9	Drinkers (means: 12 g/d in M and 3.6 g/d in W)	FFQ	448 fatal/nonfatal stroke
Misirli (2012) (Greece)	EPIC-Greece, 10.6 yr	23,601 M&W	60.5 yr for M and 57.2 yr for W	Stroke, other CVD, and cancer	9	10–50 g/d for M, 5–25 g/d for W	FFQ	395 first-ever (fatal/nonfatal) and 196 fatal stroke (95 IS and 59 HS)[b]
Chan (2013) (China)	Elderly Chinese, 5.7 yr	2735 M&W	72.3 yr	HD, stroke, and diabetes	9	10–50 g/d for M, 5–25 g/d for W	FFQ	156 fatal/nonfatal stroke
Schröder (2014) (Spain)	PREDIMED, 4.8 yr	7447 M&W with diabetes or ≥ 3 risk factors for CVD	67 yr	CVD	14	Wine consumption ≥ 700 ml/week	14-point Med-Diet adherence screener	139 fatal/nonfatal stroke
Tognon (2014) (Denmark)	MONICA, 14 yr	1849 M&W	NR (30–59 yr)	MI and stroke	8	>sex-specific medians (median among drinkers: 15.5 g/d)	7-d food record	127 nonfatal and 40 fatal stroke
Tektonidis (2015) (Sweden)	SMC, 10.4 yr	32,921 W	60.9 yr	IHD, HF, stroke, and cancer	8	5–15 g/d	FFQ	1270 IS and 262 HS (fatal/nonfatal)
Tsivgoulis (2015) (US)	REGARDS, 6.5 yr	20,197 M&W	65 yr	Stroke	9	1–7 drinks/week for W and 1–14 drinks/week for M	FFQ	565 fatal/nonfatal stroke (497 IS and 68 HS)[b]
Sherzai (2015) (US) (abstract)	CTS, 15 yr	104,268 M&W	52.9 yr	Stroke	9	NR	FFQ	3165 fatal/nonfatal stroke (2270 IS and 895 HS)
Stefler (2017) (Poland, Russia, and Czech Republic)	HAPIEE, 7 yr	19,263 M&W	56.9 yr	CVD and diabetes	9	10–50 g/d for M, 5–25 g/d for W	FFQ	109 fatal stroke

Table 1 (continued)

Author (year) (Country)	Study, follow-up duration	Participants	Mean age	Excluded patients at baseline	No. of components[a]	Moderate drinking definition	Diet assessment	Outcomes
Bonaccio (2017) (Italy)	Moli-sani, 4.3 yr	18,991 M&W	54.2 yr	CVD and diabetes	9	10–50 g/d for M, 5–25 g/d for W	FFQ	49 fatal/nonfatal stroke (16 fatal stroke)
Hirahatake (2017) (US) (abstract)	WHI, 21 yr	6031 W with T2D	NR	CVD	9	5–15 g/d	FFQ	408 fatal/nonfatal stroke
Aigner (2018) (US)	Multiethnic, 17.6 yr	172,043 M&W	59.5 yr	Stroke	9	10–25 g/d for M, 5–15 g/d for W	FFQ	3548 fatal stroke
Galbete (2018) (Germany)	EPIC-Potsdam, 10.8 yr	23,277 M&W	NR (30–65) yr	MI, stroke, diabetes, and cancer	9	10–50 g/d for M, 5–25 g/d for W	FFQ	321 fatal/nonfatal stroke (259 IS)
Veglia (2018) (5 European countries)	IMPROVE, 3.0 yr	3707 M&W	64.2 (55–79) yr	CVD	7	Wine consumption 1–2 glasses/d	FFQ	73 fatal/nonfatal stroke[b]
Paterson[c] (2018) (UK)	EPIC-Norfolk, 17.0	23,232 M&W	59.1 (40–77) yr	Stroke	9	10–50 g/d for M, 5–25 g/d for W	7-d food record	2009 fatal/nonfatal stroke
SCHS (unpublished) (Singapore)	SCHS, 17 yr	57,078 M&W	56.1 yr	Cancer, heart attack or angina, and stroke	9	10–25 g/d for M, 5–15 g/d for W	FFQ	1413 fatal stroke (1072 IS/unspecified[d] and 341 HS)
SUN (unpublished) (Spain)	SUN, 17 yr	12,670 M&W	42.6 yr	CVD	9	10–50 g/d for M, 5–25 g/d for W	FFQ	103 fatal/nonfatal stroke

CHD coronary heart disease, *CTS* California Teachers Study, *CVD* cardiovascular disease, *EPIC* European Prospective Investigation into Cancer and Nutrition, *FFQ* food frequency questionnaire, *HAPIEE* Health Alcohol and Psychosocial Factors in Eastern Europe, *HS* hemorrhagic stroke, *IHD* ischemic heart disease, *IMPROVE* Carotid Intima Media Thickness (IMT) and IMT-Progression as Predictors of Vascular Events in a High Risk European Population, *IS* ischemic stroke, *M* men, *MedDiet* Mediterranean diet, *MI* myocardial infarction, *MONICA* MONItoring trends and determinants of Cardiovascular disease, *NHS* Nurses' Health Study, *NL* Netherlands, *NOMAS* Northern Manhattan Study, *NR* not reported, *PREDIMED* Prevención con Dieta Mediterránea trial, *REGARDS* REasons for Geographic and Racial Differences in Stroke, *SCHS* Singapore Chinese Health Study, *SMC* Swedish Mammography Cohort, *T2D* type 2 diabetes, *W* women, *WHI* Women's Health Initiative, *yr* years

[a]Most studies used medians as cutoffs for food components and assigned each component 0 or 1 point, with three exceptions: the study by Schröder et al. used specific predefined cutoffs and assigned each 0 or 1 point; the study by Galbete et al. used tertiles and assigned each 0, 1, or 2 points; and the study by Veglia et al. used tertiles and assigned each 0 or 1 (1 point for top tertile of potentially beneficial components and for bottom tertile of potentially detrimental components)

[b]Including a small proportion of patients with transient ischemic attack or other cerebrovascular disease

[c]Including Sweden, the Netherlands, Italy, France, and Finland

[d]According to a pilot study of 308 cases with medical records in the SCHS, 86% of the unspecified stroke cases were ischemic stroke

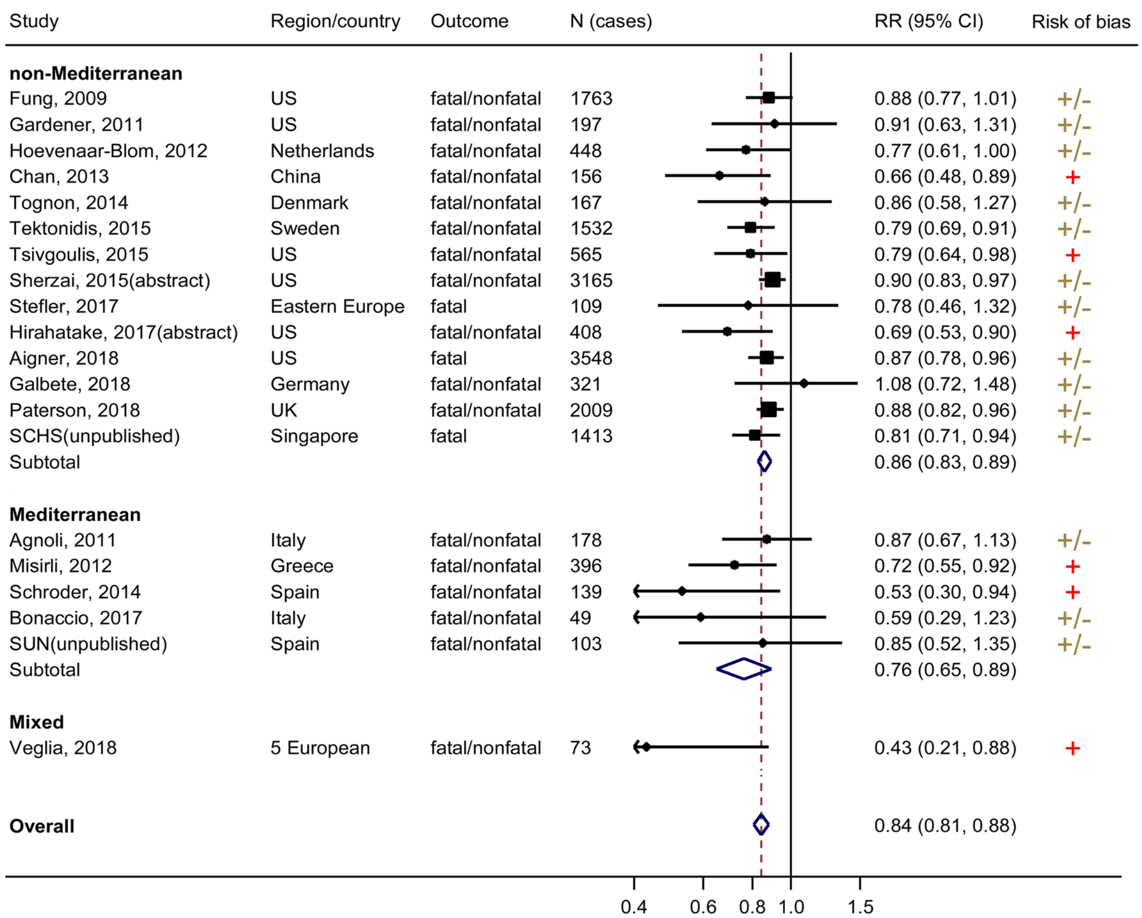

Fig. 2 Meta-analysis of the Mediterranean diet score (each 4-point increment) and risk of stroke for the studies of Mediterranean and non-Mediterranean populations. SCHS, Singapore Chinese Health Study; SUN, Seguimiento Universidad de Navarra (University of Navarra follow-up). "±" indicates moderate risk of bias, and "+" indicates serious risk of bias (see Supplemental Table 9)

transient ischemic attack (RR 0.86, 95% CI 0.83–0.89), or omitting the three studies [20, 21, 36] that included high-risk participants (RR 0.86, 95% CI 0.83–0.89). A total of 18 studies reported results based on extreme categories (tertile, quartile or quintile) of the MedDiet score, and the summary RRs comparing the highest with the lowest categories of the MedDiet score were 0.84 (95% CI 0.80–0.88) for all studies, 0.84 (95% CI 0.80–0.88) for studies from non-Mediterranean regions, and 0.74 (95% CI 0.60–0.92) for studies from the Mediterranean regions (Supplemental Figure 2). The summary estimates for total, ischemic or hemorrhagic stroke were not sensitive to any single study included in the respective analyses (data not shown).

Publication bias

Both Egger ($P = 0.004$) and Begg tests ($P = 0.01$) suggested possible publication bias for the dose–response meta-analysis of the MedDiet and risk of stroke. Visual inspection of funnel plots also suggested asymmetry (Supplemental Figure 3). However, publication bias was less evident when limiting to the 14 studies without potentially serious risk of bias ($P_{\text{Egger}} = 0.28$; $P_{\text{Begg}} = 0.13$) (Supplemental Figure 3).

Discussion

In this meta-analysis of 20 published and unpublished prospective studies that included over 16,000 stroke cases, adherence to the MedDiet was significantly associated with a lower risk of stroke. Each 4-point increment in the MedDiet score, approximately the difference between the lowest and the highest quintiles of the score in the included studies, was associated with 16% lower risk of stroke, with similar risk reductions observed for ischemic stroke and hemorrhagic stroke. The inverse association between the MedDiet score and risk of stroke did not differ substantially by version of the score and was not affected by the varying definition of moderate drinking across studies. The MedDiet was

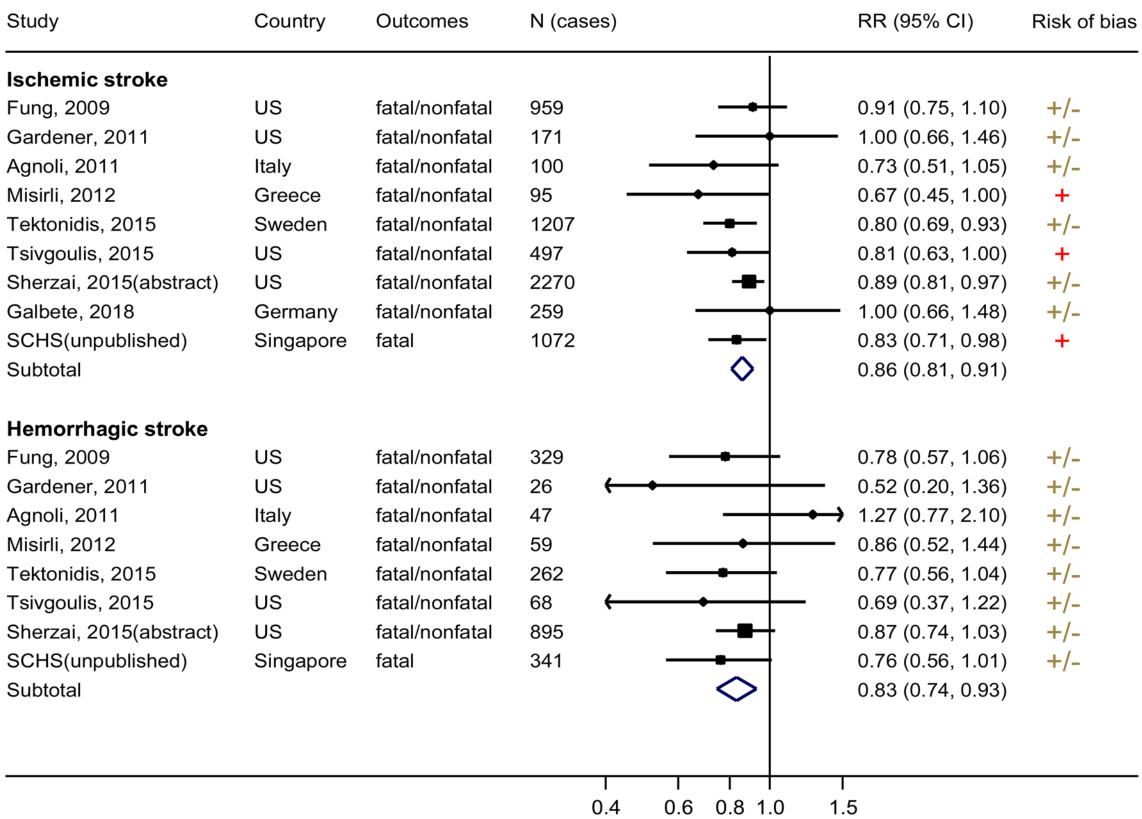

Fig. 3 Meta-analysis of the Mediterranean diet score (each 4-point increment) and risk of ischemic and hemorrhagic stroke. SCHS, Singapore Chinese Health Study. "±" indicates moderate risk of bias, and "+" indicates serious risk of bias (see Supplemental Table 9)

associated with a lower risk of stroke in both Mediterranean and non-Mediterranean populations.

Several previous meta-analyses [7, 9, 11–13] have examined the association between the MedDiet and risk of stroke. Although all of them reported a significant inverse association, only six or fewer prospective studies were included in any single analysis, and all but one [13] have been unable to investigate the association by stroke subtype and by version of the MedDiet index. In one of the most recent meta-analysis by Rosato et al. [13], the MedDiet was associated with lower risk of ischemic (five studies) but not hemorrhagic stroke (four studies), and only the Trichopoulou et al's index (four studies) was associated with lower stroke risk. Of the six studies included in the Rosato et al's analyses of total stroke, one [47] was a hospital-based case–control study prone to recall and selection bias, and another [48] evaluated changes in MedDiet scores rather than absolute values of the score. Thus, the combined results from this previous meta-analysis need to be cautiously interpreted.

In our meta-analysis, the inverse association between the MedDiet and stroke risk appeared somewhat stronger in Mediterranean than in non-Mediterranean studies. While this regional difference in association was not significant, the number of cases in the Mediterranean studies was small, and it remains possible that certain unique dietary component such as olive oil contributed to the potentially additional protection of the MedDiet on stroke in Mediterranean populations [49, 50]. It is also possible that serving sizes of typical foods of the MedDiet (e.g. fruit, salads, vegetables, nuts, and olive oil) are larger such that each unit increment of the MedDiet score is associated with larger difference in the consumption of these foods in Mediterranean regions than in non-Mediterranean regions.

Our findings showed that both Trichopoulou et al's and Fung et al's MedDiet indices were associated with a lower risk of stroke. This consistency in results is plausible because both indices encompass key dietary components that may lower stroke risk, for example higher consumption of fruit, vegetables, nuts and fish, lower consumption of meat products (in particular red meat and processed meat), and avoidance of excessive drinking [51, 52]. As a result, a higher score of both indices was associated with a diet abundant in dietary fiber, B-group vitamins, carotenoids, flavonoids and minerals (e.g. magnesium and potassium), and low in heme iron and *trans*-fat, all of which may contribute to the reduction of stroke, independently or jointly [53, 54]. Although the MedDiet is not a sodium-lowering diet, adhering to this diet is also likely to result in a reduction of

Table 2 Subgroup analysis for the meta-analysis of the Mediterranean diet score (4-point increment) and stroke risk

	No. of studies	No. of cases	RR (95% CI)	*P*-het	I^2 (%)	*P*-differ
Baseline age (years)[a]						
< 65	15	15,274	0.86 (0.83–0.90)	0.54	0	–
≥ 65	4	1057	0.75 (0.63–0.89)	0.34	11.1	0.13
Sex						
Men	3	1959	0.74 (0.62–0.89)	0.27	23.5	–
Women	7	8882	0.84 (0.78–0.90)	0.26	22.3	0.29
Duration (years)						
< 10	8	1466	0.76 (0.67–0.86)	0.40	4.4	–
10 to < 15	5	2864	0.80 (0.72–0.88)	0.47	0	0.56
≥ 15	7	12,409	0.87 (0.83–0.91)	0.57	0	0.06
No. of cases						
< 200	9	1171	0.77 (0.67–0.88)	0.46	0	–
200 to < 500	4	1573	0.78 (0.66–0.92)	0.23	30.4	0.97
≥ 500	7	13,995	0.87 (0.83–0.90)	0.62	0	0.12
Outcome						
Fatal	8	6114	0.86 (0.80–0.92)	0.92	0.0	–
Non-fatal	1	1480	0.89 (0.77–1.03)	NA	NA	NA
Fatal and non-fatal	17	11,669	0.83 (0.79–0.88)	0.19	22.7	0.74
Serious risk of bias (ROBINS-I)						
No (total stroke)	14	15,002	0.87 (0.83–0.90)	0.88	0	–
Yes (total stroke)	6	1737	0.70 (0.62–0.80)	0.53	0	**0.005**
No (ischemic stroke)	6	4966	0.87 (0.82–0.93)	0.62	0	–
Yes (ischemic stroke)	3	1664	0.81 (0.71–0.91)	0.62	0	0.32
Region[b]						
Mediterranean	5	865	0.76 (0.55–0.89)	0.49	0	–
Other Europe	6	4586	0.86 (0.80–0.91)	0.52	0	0.24
US	6	9646	0.87 (0.83–0.92)	0.48	0.0	0.15
Asia	2	1569	0.77 (0.64–0.92)	0.24	28.6	0.85
All non-Mediterranean	14	15,801	0.86 (0.83–0.89)	0.48	0	0.17
Version of the MedDiet[c]						
Trichopoulou et al.	13	7863	0.87 (0.83–0.91)	0.58	0	–
Fung et al.	5	8664	0.83 (0.78–0.89)	0.41	0	0.34
Other	2	212	0.49 (0.31–0.76)	0.66	0	0.07
Definition of moderate drinking[d]						
Definition (A)	8	3321	0.84 (0.77–0.92)	0.36	9.0	–
Definition (B)	5	8664	0.83 (0.78–0.89)	0.41	0	0.61
Other	7	4754	0.82 (0.72–0.92)	0.17	34.1	0.96
Excluding other major CVD						
No	4	9287	0.88 (0.84–0.92)	0.72	0	–
Yes	16	7452	0.80 (0.75–0.85)	0.48	0	**0.03**
Adjustment for potential mediators[e]						
No	5	2665	0.85 (0.77–0.95)	0.91	0.0	–
Yes	15	14,074	0.83 (0.78–0.88)	0.12	31.6	0.83

The bold *P* values indicate that there were significant differences in the association between the subgroup populations

CVD cardiovascular disease, *MedDiet* Mediterranean diet, *NA* not applicable, *P-het P* value for heterogeneity test, *P-differ P* value for difference by meta-regression, *ROBINS-I* Risk Of Bias In Non-randomized Studies-of Interventions, – reference group

[a]Mean age at baseline. One study was excluded because age information was not reported

[b]Mediterranean region includes Italy, Greece and Spain; Other Europe indicates other non-Mediterranean region in Europe. One study included participants from both regions were not included in this analysis

[c]Both Trichopoulou et al. and Fung et al. included moderate drinking and higher intakes of fruit, vegeta-

Table 2 (continued)

bles, nut, legume and fish as beneficial components, while in a few cases two of these components were combined as one. The major characteristics for distinguishing the two versions were that Trichopoulou et al. used total cereals as a beneficial component and total meat and total dairy as detrimental components, whereas Fung et al. included whole grain and red and processed meat, and excluded the dairy item

[d]For definition (A), moderate drinking was defined as alcohol consumption of 5-25 g/day in women and 10-50 g/day in men; for definition (B), moderate drinking was defined as 5–10 g/day in women and 10–25 g/day in men

[e]Adjustment for either blood pressure or blood lipids

dietary sodium because of the lower consumption of processed foods.

We observed similar associations for ischemic stroke and hemorrhagic stroke. For most components of the MedDiet, the associations with hemorrhagic stroke have been investigated less and evidence is less conclusive as compared with the associations with ischemic stroke [53, 54], which might be partly due to the much lower incidence of hemorrhagic stroke in most populations [2]. In a large case–control study [5] that included 2337 new-onset ischemic stroke and 663 intracerebral hemorrhagic stroke cases from 22 countries worldwide, a higher score of an "unhealthy cardiovascular diet" (defined by higher consumption of meat, salty snacks and fried foods, and lower consumption of fruit and green leafy, cooked or raw vegetables) was associated with higher risk of both types of stroke. Results from a national analysis of the US population suggested that suboptimal diets were associated with a large proportion of deaths from both ischemic stroke (44.5%) and hemorrhagic stroke (60.9%) in 2012 [6]. In our meta-analysis, seven of the eight studies on the MedDiet and risk of hemorrhagic stroke showed inverse associations, but no any single association was statistically significant. However, our combined analysis included over 2000 hemorrhagic stroke cases and therefore had sufficient statistical power to detect a moderate association between the MedDiet and risk of hemorrhagic stroke.

Our findings are in agreement with results from human intervention trials evaluating the cardiovascular effects of the MedDiet. In the large Spanish PREDIMED (Prevencion con Dieta Mediterranea) trial of high-risk population free of CVD [10], long-term intervention with the MedDiet (median: 4.8 years), combined with mixed nuts or extra-virgin olive oil, substantially reduced risk of stroke by ~ 40% as compared with a low-fat diet. Accumulating evidence from randomized controlled trials shows that the MedDiet intervention resulted in reduced body weight, blood pressure and plasma glucose, and improved lipid profiles such as decreased LDL cholesterol and increased HDL cholesterol [55–58]. Of note is that in our meta-analysis, estimates of association were adjusted for indices of adiposity in most of the included studies, and the combined estimates were similar after restricting to studies with adjustment for potential mediators (blood lipids and blood pressure). These results suggest that other mechanisms may be involved in the link between MedDiet and stroke, such as protection against inflammation, oxidative stress, platelet aggregation and endothelial dysfunction, and favorable alternation of gut microbiota-derived metabolites affecting cardiovascular health [59, 60].

Our meta-analysis presents several strengths, including the collection of both published and unpublished prospective studies from North American, Europe and Eastern Asia, the large number stroke (and subtype-specific stroke) cases, and the comprehensive assessment of the potential influences of important methodological characteristics (e.g. version of the MedDiet index) on the examined association.

Several limitations also merit discussion. First, our meta-analysis of observational studies is subject to residual confounding. However, in most primary studies, results were adjusted for socio-demographic and other lifestyle factors. The consistency in findings across cohorts of diverse regions and concordance between our findings and those from the PREDIMED trial and trials of intermediate outcomes suggest that residual confounding is not fully responsible for the observed inverse association between the MedDiet and stroke risk. Second, diet information was mostly recorded using food frequency questionnaires in the primary studies, and in all except for one study [19] the dietary score was calculated from a single measurement of dietary habits. Third, we were unable to further investigate the impact of the MedDiet on subtypes of ischemic stroke (e.g. large-artery, small-vessel, and cardioembolic stroke) and hemorrhagic stroke (e.g. intracerebral and subarachnoid hemorrhage). Given the heterogeneous etiologies for these specific types of stroke [61, 62], future studies with more detailed diagnostic information are warranted. Finally, there was evidence of a possible publication bias. Notwithstanding, our meta-analysis included published full reports, conference abstracts and also unpublished cohorts, and the combined result from larger studies (> 500 cases) was comparable to the overall result of the meta-analysis. Furthermore, when considering only studies that did not have potentially serious risk of bias, the combined results were essentially unchanged, but publication bias was less evident.

The morbidity and mortality of stroke is increasing in many countries worldwide, highlighting the urgent need for effective prevention strategies [1]. Results of our meta-analysis showed that adhering to the Mediterranean diet, a relatively simple eating pattern featuring abundant minimally processed plant foods, low consumption of red and processed meat and moderate alcohol consumption, was associated with lower risk of stroke in both Mediterranean and non-Mediterranean populations, and for both ischemic stroke and hemorrhagic stroke. These findings support the promotion of the Mediterranean diet as an important dietary approach for the global prevention of stroke.

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Compliance with ethical standards

Conflict of interest No conflict of interest existed for any of the authors.

References

1. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. Circ Res. 2017;120(3):439–48.
2. Feigin VL, Krishnamurthi RV, Parmar P, et al. Update on the global burden of ischemic and hemorrhagic stroke in 1990–2013: the GBD 2013 study. Neuroepidemiology. 2015;45(3):161–76.
3. Roth GA, Forouzanfar MH, Moran AE, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. N Engl J Med. 2015;372(14):1333–41.
4. Feigin VL, Roth GA, Naghavi M, et al. Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol. 2016;15(9):913–24.
5. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010;376(9735):112–23.
6. Micha R, Penalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. JAMA. 2017;317(9):912–24.
7. Galbete C, Schwingshackl L, Schwedhelm C, Boeing H, Schulze MB. Evaluating Mediterranean diet and risk of chronic disease in cohort studies: an umbrella review of meta-analyses. Eur J Epidemiol. 2018;33(10):909–31.
8. Salas-Salvado J, Guasch-Ferre M, Lee CH, Estruch R, Clish CB, Ros E. Protective effects of the Mediterranean diet on type 2 diabetes and metabolic syndrome. J Nutr. 2016;146:920S–7S.
9. Grosso G, Marventano S, Yang J, et al. A comprehensive meta-analysis on evidence of Mediterranean diet and cardiovascular disease: are individual components equal? Crit Rev Food Sci Nutr. 2017;57(15):3218–32.
10. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med. 2018;378(25):e34.
11. Kontogianni MD, Panagiotakos DB. Dietary patterns and stroke: a systematic review and re-meta-analysis. Maturitas. 2014;79(1):41–7.
12. Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. Ann Neurol. 2013;74(4):580–91.
13. Rosato V, Temple NJ, La Vecchia C, Castellan G, Tavani A, Guercio V. Mediterranean diet and cardiovascular disease: a systematic review and meta-analysis of observational studies. Eur J Nutr. 2017.
14. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA. 2000;283(15):2008–12.
15. Hankin JH, Stram DO, Arakawa K, et al. Singapore Chinese Health Study: development, validation, and calibration of the quantitative food frequency questionnaire. Nutr Cancer. 2001;39(2):187–95.
16. Pan A, De Silva DA, Yuan JM, Koh WP. Sleep duration and risk of stroke mortality among Chinese adults: Singapore Chinese health study. Stroke. 2014;45(6):1620–5.
17. Martinez-Gonzalez MA, Sanchez-Villegas A, De Irala J, Marti A, Martinez JA. Mediterranean diet and stroke: objectives and design of the SUN project. Seguimiento Universidad de Navarra. Nutr Neurosci. 2002;5(1):65–73.
18. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003;348(26):2599–608.
19. Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. Circulation. 2009;119(8):1093–100.
20. Hirahatake KM. Diet quality and cardiovascular disease risk in postmenopausal women with type 2 diabetes: the women's health initiative. Circulation. 2017;135(Suppl 1):A14 **(Abstract)**.
21. Schroder H, Salas-Salvado J, Martinez-Gonzalez MA, et al. Baseline adherence to the Mediterranean diet and major cardiovascular events: prevencion con Dieta Mediterranea trial. JAMA Intern Med. 2014;174(10):1690–2.
22. Paterson KE, Myint PK, Jennings A, et al. Mediterranean diet reduces risk of incident stroke in a population with varying cardiovascular disease risk profiles. Stroke. 2018;49:2415–20.
23. Tong TY, Wareham NJ, Khaw KT, Imamura F, Forouhi NG. Prospective association of the Mediterranean diet with cardiovascular disease incidence and mortality and its population impact in a non-Mediterranean population: the EPIC-Norfolk study. BMC Med. 2016;14(1):135.
24. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
25. Bonaccio M, Di Castelnuovo A, Pounis G, et al. High adherence to the Mediterranean diet is associated with cardiovascular protection in higher but not in lower socioeconomic groups: prospective findings from the Moli-sani study. Int J Epidemiol. 2017;46(5):1478–87.
26. Aigner A, Becher H, Jacobs S, et al. Low diet quality and the risk of stroke mortality: the multiethnic cohort study. Eur J Clin Nutr. 2018;72(7):1035–45.
27. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol. 1992;135(11):1301–9.

28. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. Stata J. 2006;6(1):40.
29. Hamling J, Lee P, Weitkunat R, Ambuhl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med. 2008;27(7):954–70.
30. Agnoli C, Krogh V, Grioni S, et al. A priori-defined dietary patterns are associated with reduced risk of stroke in a large Italian cohort. J Nutr. 2011;141(8):1552–8.
31. Stefler D, Malyutina S, Kubinova R, et al. Mediterranean diet score and total and cardiovascular mortality in Eastern Europe: the HAPIEE study. Eur J Nutr. 2017;56(1):421–9.
32. Chan R, Chan D, Woo J. The association of a priori and a posterior dietary patterns with the risk of incident stroke in Chinese older people in Hong Kong. J Nutr Health Aging. 2013;17(10):866–74.
33. Gardener H, Wright CB, Gu Y, et al. Mediterranean-style diet and risk of ischemic stroke, myocardial infarction, and vascular death: the Northern Manhattan Study. Am J Clin Nutr. 2011;94(6):1458–64.
34. Tektonidis TG, Akesson A, Gigante B, Wolk A, Larsson SC. A Mediterranean diet and risk of myocardial infarction, heart failure and stroke: a population-based cohort study. Atherosclerosis. 2015;243(1):93–8.
35. Tsivgoulis G, Psaltopoulou T, Wadley VG, et al. Adherence to a Mediterranean diet and prediction of incident stroke. Stroke. 2015;46(3):780–5.
36. Veglia F, Baldassarre D, de Faire U, et al. A priori-defined Mediterranean-like dietary pattern predicts cardiovascular events better in north Europe than in Mediterranean countries. Int J Cardiol. 2018.
37. Tognon G, Lissner L, Saebye D, Walker KZ, Heitmann BL. The Mediterranean diet in relation to mortality and CVD: a Danish cohort study. Br J Nutr. 2014;111(1):151–9.
38. Galbete C, Kroger J, Jannasch F, et al. Nordic diet, Mediterranean diet, and the risk of chronic diseases: the EPIC-Potsdam study. BMC Med. 2018;16(1):99.
39. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88.
40. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol. 2012;175(1):66–73.
41. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58.
42. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088–101.
43. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34.
44. Hoevenaar-Blom MP, Nooyens AC, Kromhout D, et al. Mediterranean style diet and 12-year incidence of cardiovascular diseases: the EPIC-NL cohort study. PLoS ONE. 2012;7(9):e45458.
45. Misirli G, Benetou V, Lagiou P, Bamia C, Trichopoulos D, Trichopoulou A. Relation of the traditional Mediterranean diet to cerebrovascular disease in a Mediterranean population. Am J Epidemiol. 2012;176(12):1185–92.
46. Sherzai AZ, Ma H, Horn-Ross P, et al. Mediterranean diet and incidence of stroke in the California teachers study. Circulation. 2015;131(1):AMP85 **(Abstract)**.
47. Yau WY, Hankey GJ. Which dietary and lifestyle behaviours may be important in the aetiology (and prevention) of stroke? J Clin Neurosci. 2011;18(1):76–80.
48. Sotos-Prieto M, Bhupathiraju SN, Mattei J, et al. Changes in diet quality scores and risk of cardiovascular disease among US men and women. Circulation. 2015;132(23):2212–9.
49. Martinez-Gonzalez MA, Dominguez LJ, Delgado-Rodriguez M. Olive oil consumption and risk of CHD and/or stroke: a meta-analysis of case-control, cohort and intervention studies. Br J Nutr. 2014;112(2):248–59.
50. Ruiz-Canela M, Martinez-Gonzalez MA. Olive oil in the primary prevention of cardiovascular disease. Maturitas. 2011;68(3):245–50.
51. Larsson SC, Wallin A, Wolk A, Markus HS. Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. BMC Med. 2016;14(1):178.
52. Bechthold A, Boeing H, Schwedhelm C, et al. Food groups and risk of coronary heart disease, stroke and heart failure: a systematic review and dose-response meta-analysis of prospective studies. Crit Rev Food Sci Nutr. 2017:1–20.
53. Larsson SC. Dietary approaches for stroke prevention. Stroke. 2017;48(10):2905–11.
54. Iacoviello L, Bonaccio M, Cairella G, et al. Diet and primary prevention of stroke: systematic review and dietary recommendations by the ad hoc Working Group of the Italian Society of Human Nutrition. Nutr Metab Cardiovasc Dis. 2018;28(4):309–34.
55. Esposito K, Kastorini CM, Panagiotakos DB, Giugliano D. Mediterranean diet and weight loss: meta-analysis of randomized controlled trials. Metab Syndr Relat Disord. 2011;9(1):1–12.
56. Gay HC, Rao SG, Vaccarino V, Ali MK. Effects of different dietary interventions on blood pressure: systematic review and meta-analysis of randomized controlled trials. Hypertension. 2016;67(4):733–9.
57. Kastorini CM, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. J Am Coll Cardiol. 2011;57(11):1299–313.
58. Schwingshackl L, Chaimani A, Schwedhelm C, et al. Comparative effects of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: a systematic review and network meta-analysis. Crit Rev Food Sci Nutr. 2018:1–14.
59. Tosti V, Bertozzi B, Fontana L. Health benefits of the Mediterranean diet: metabolic and molecular mechanisms. J Gerontol A Biol Sci Med Sci. 2018;73(3):318–26.
60. Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. Nutr Metab Cardiovasc Dis. 2014;24(9):929–39.
61. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(12):3754–832.
62. Traylor M, Farrall M, Holliday EG, et al. Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE collaboration): a meta-analysis of genome-wide association studies. Lancet Neurol. 2012;11(11):951–62.

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