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ORIGINAL CONTRIBUTION

Mediterranean diet and cardiovascular disease: a systematic review and meta-analysis of observational studies

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Abstract

Purpose To provide evidence of the relationship of Mediterranean diet (MD) on incidence/mortality for cardiovascular disease (CVD), coronary/ischemic heart disease (CHD)/acute myocardial infarction (AMI) and stroke (ischemic/hemorrhagic) by sex, geographic region, study design and type of MD score (MDS).

Methods We performed a systematic review and meta-analysis of observational studies. Pooled relative risks (RRs) were calculated using random-effects models.

Results We identified 29 articles. The RR for the highest versus the lowest category of the MDS was 0.81 (95% CI 0.74–0.88) for the 11 studies that considered unspecified CVD, consistent across all strata. The corresponding pooled RR for CHD/AMI risk was 0.70 (95% CI 0.62–0.80), based on 11 studies. The inverse relationship was consistent across strata of study design, end point (incidence and mortality), sex, geographic area, and the MDS used. The overall RR for the six studies that considered unspecified stroke was 0.73 (95% CI 0.59–0.91) for the highest versus the lowest category of the MDS. The corresponding values were 0.82 (95% CI 0.73–0.92) for ischemic (five studies) and 1.01 (95% CI 0.74–1.37) for hemorrhagic stroke (four studies).

Conclusions Our findings indicate and further quantify that MD exerts a protective effect on the risk of CVD. This inverse association includes CHD and ischemic stroke, but apparently not hemorrhagic stroke.

Keywords Cardiovascular disease · Coronary heart disease · Mediterranean diet · Meta-analysis · Stroke

Abbreviations

MD	Mediterranean diet
CVD	Cardiovascular disease
CHD	Coronary heart disease
AMI	Acute myocardial infarction
MDS	Mediterranean diet score
RR	Relative risk
TS	Trichopoulou score
LDL	Low-density lipoprotein
HDL	High-density lipoprotein

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Introduction

The Mediterranean diet (MD) is the traditional dietary style of several countries around the Mediterranean Sea. Although the MD varies from one country to another, its key traditional features are: high consumption of grains and cereals (traditionally mainly whole grains), legumes, fruits, nuts, vegetables, and fish; use of olive oil as the main fat, with the consequent high monounsaturated/saturated fat ratio; moderate consumption of milk and dairy products; a low-to-moderate wine consumption (mainly at meals); and low consumption of meat and meat products. An *a* priori score to estimate the adherence to MD has been developed by Trichopoulou et al. [1] (TS), and is now commonly used

together with some variants developed to better estimate MD adherence in non-Mediterranean countries [2, 3].

The MD has been associated with several benefits [4] such as reduced total mortality [5] and reduced risk of several diseases, including selected cancers [5, 6], cognitive impairment [7, 8], and the metabolic syndrome and its components, such as obesity, hypertension, hyperglycemia and hyperlipidemia [9].

Many observational studies have examined the relationship between MD and cardiovascular disease (CVD) incidence and mortality [10–12]. Their risk estimates have been summarized in a few meta-analyses [5, 7, 8, 12–14], which overall showed an inverse relationship. However, most meta-analyses have methodological limitations [15], including the lack of a complete literature search, the inclusion of duplicate studies, the lack of sensitivity analyses, and the lack of stratification by geographic area where the study was conducted (Mediterranean/non-Mediterranean country). Other notable limitations of previous meta-analyses are the omission of case–control studies and a failure to analyze studies in terms of different types of CVD (particularly stroke subtypes). This systematic review and meta-analysis provides quantitative evidence of the relationship of MD on incidence/mortality for CVD, coronary/ischemic heart disease (CHD)/acute myocardial infarction (AMI) and stroke (ischemic/hemorrhagic), by sex, geographic region, study design and type of MD score (MDS).

Materials and methods

Search strategy

We conducted a systematic literature search in the Medline database of studies published up to August 2016. The following search string was used: "Cardiovascular Diseases [Mesh] AND Mediterranean AND diet" without restrictions on language or publication date. Two authors (VG and AT) independently assessed the retrieved articles for inclusion/exclusion criteria. They also checked the reference list of pertinent papers to identify further studies. Abstracts and unpublished studies were not included. No studies were excluded a priori for weakness of design or data quality.

Eligibility criteria

We used eligibility criteria based on the PICOS (participants/population, intervention/exposure(s), comparator(s)/control, outcome(s), and study design) approach as follows: (1) participants: free of previous cardiovascular events, living in either Mediterranean or non-Mediterranean areas; (2) exposure: adherence to MD, assessed by an a priori MDS (TS or other); (3) comparators: population with a lower MD adherence, adjusted relative risk (RR) estimates with their confidence intervals (CIs); (4) outcomes: CHD, AMI, stroke (ischemic, hemorrhagic, or unspecified), and unspecified CVD; and (5) study design: case–control or cohort study.

Data extraction

Data extraction was undertaken independently by two authors (VG and VR). Any disagreement was resolved by discussion. We extracted the following information: last name of the first author, year of publication, location, study design (case–control or cohort study), number of subjects (cases and controls/non-cases/cohort size), sex, period of enrolment and follow-up, age, outcome (CHD/AMI, stroke, CVD), mortality or incidence study, type of MDS (TS or other) and range of score, effect estimator used, i.e., odds ratio (OR), RR, hazard ratio (HR), risk estimate (both categorically and continuously), and covariates adjusted for.

Statistical analysis

To assess the relationship between adherence to MD and CVD, summary estimates of the RR were calculated using DerSimonian and Laird random-effects models, that consider both within- and between-study variability [16]. We combined the risk estimates (RR, HR or OR) for the highest compared with the lowest category of the MDS from each cohort or case–control study. Studies were grouped according to the different clinical outcomes (CHD/AMI, ischemic or hemorrhagic stroke, unspecified CVD). We pooled together studies reporting incidence or mortality estimates, since by fitting meta-regression models we found no heterogeneity across strata of incidence or mortality for all the outcomes. When a study reported both incidence and mortality estimates separately, the incidence estimate was considered [17–19]. When a study [18, 20, 21] reported various estimates for various outcomes, we pooled these estimates using Hamling's method to manipulate non-independent risk ratio [22]. The RRs adjusted for the largest number of confounding factors were included in all the analyses. For a study [23] reporting third quintile as reference category, we computed the RR for the fifth versus the first quintile and, to obtain the 95% CI, we calculated the approximate covariance matrix using generalized least squares [24, 25]. We included risk estimates for men and women combined, and if a study reported separate risk estimates [26, 27], we pooled them using the fixed effect models. We present the main combined estimates using forest plots.

We assessed heterogeneity among studies using the χ^2 test (defined as significant for a p value < 0.10) [28] and quantified the inconsistencies using the I^2 statistic [29, 30]. Subgroup analyses were performed by study design (case–control or cohort studies), end point (i.e., mortality

or incidence), sex, geographic area of the study population (Mediterranean or non-Mediterranean countries), and type of MDS (TS or others). The overall RR for an increment of 1 point in the MDS was computed only for studies using the TS, by pooling the corresponding study-specific RRs with random-effects models [16]. When studies reported RRs for an increment of 2 points, the increment for 1 point was obtained by dividing the natural logarithm estimate by 2. When the increment was not reported in the original study, we computed it for studies reporting three or more categories of MDS [26, 31] using the method proposed by Greenland and Longnecker [24, 25].

To investigate the influence of single studies on the overall results, we conducted a sensitivity analysis in which one study at a time was removed. Publication bias was assessed by Begg's and Mazumdar's and Egger's tests [32, 33]. All the analyses were performed using the STATA statistical package (version 13; StataCorp, College Station, TX, USA).

Results

A total of 1264 publications was obtained up to August 2016 (Fig. 1). On the basis of the titles and abstracts we excluded 1041 of them. We retrieved the full text of 223 publications and then excluded 178 of them because they did not report data on the association between the adherence to the MD and the outcomes of interest. We identified two additional publications by scanning the reference lists of the retrieved publications [26, 34]. Of the remaining 47 publications, we further excluded 18 of them: 4 because of their cross-sectional design [35–37], 6 because they evaluated the relationship between adherence to the MD and secondary prevention of CVD [1, 38–42], 2 because they had been conducted on patients at high risk of CVD [43, 44], and 1 because it did not report the adjusted estimates [45]. When multiple reports were published on the same study population and they did not provide further information for stratified analyses [18, 23, 27, 46–54], we included only the most informative one [23, 27, 47, 48, 50, 52]; this resulted in the exclusion of five additional publications.

We identified 29 articles (based on 5 case–control and 21 cohort studies, as some studies considered various outcomes in different articles and some articles considered two cohorts), published from 1995 to 2016, that reported a quantitative relationship between MD adherence and CVD. The main characteristics and findings of these studies (from now we use the word study as a synonym of article) are reported in Table 1. The TS was used to assess the adherence to the MD in 12 studies, while 16 studies used alternative MDSs. The components included in the MDS in each study are listed in supplementary Table S1.

The pooled RR for CHD/AMI risk for the highest versus the lowest category of the MDS was 0.70 (95% CI 0.62–0.80), based on 11 studies (Fig. 2). The inverse relationship was consistent across strata of study design (RR 0.74 for cohort and 0.41 for case–control studies), end point (RR 0.62 for incident and 0.59 for fatal CHD/AMI), sex (RR 0.70 for women and 0.67 for men), geographic area (RR 0.61 for Mediterranean and 0.79 for non-Mediterranean countries), and the MDS used (RR 0.68 for TS and 0.72 for alternative scores) (Table 2).

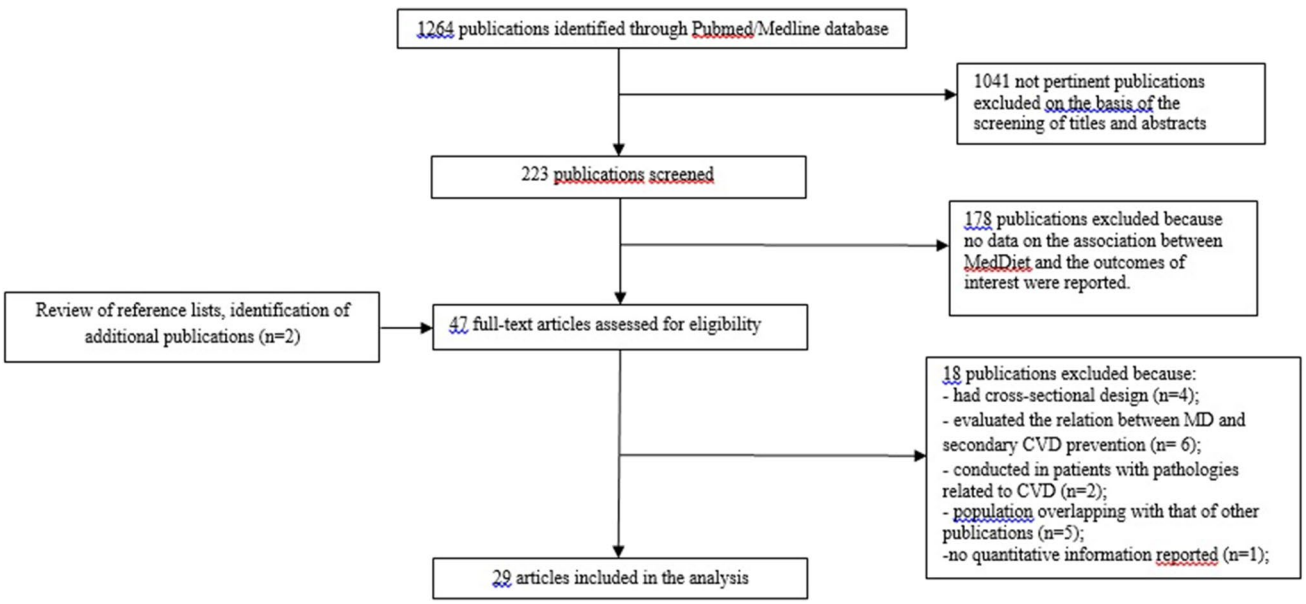

Fig. 1 Flow chart of process of the selection of epidemiological studies. *CVD* cardiovascular disease, *MD* Mediterranean diet

Table 1 Main characteristics of the observational studies on the relation between adherence to Mediterranean diet and cardiovascular disease

First author (study name)	Country	Time recruitment/ Follow-up duration (years)	*N* cases/cohort size or *N* controls	Age at recruitment (years)	Disease (outcome)	MDS, range	Risk estimate (95% confidence interval), highest versus lowest MDS
Cohort studies							
Agnoli et al. 2011 (EPIC-Italy) [31]	Italy	1993–1998/7.89 (mean)	178/40,681	35–74	Stroke	TS, 0–9	HR = 0.82 (0.57–1.19) 6–9 versus 0–4
			100/40,681		Ischemic stroke		HR = 0.82 (0.57–1.19) 6–9 versus 0–4
			47/40,681		Hemorrhagic stroke		HR = 0.82 (0.57–1.19) 6–9 versus 0–4
Bellavia et al. 2016 (Cohort of Swedish Men and Swedish Mammography cohort) [55]	Sweden	1987–1990/ 15	4153/71,333	45–83	CVD (Mortality)	TS modified, 0–8	HR = 0.74 (0.65–0.84) 6–8 versus 0–2 HR = 0.59 (0.48–0.72) 1-point increment
Bertoia et al. 2014 (Women Health Initiative) [56]	USA	1993–1998/ 10.5 (mean)	237/93,122 W (postmenopause)	50–79	Cardiac death (Mortality)	TS modified 0–40	HR = 0.67 (0.46–0.99) 25–40 versus 3–16
Buckland et al. 2009 (EPIC-Spain) [57]	Spain	1992–1996/ 10.4 (mean)	606/41,078	29–69	CHD	TS, 0–18	HR = 0.60 (0.47–0.77) 11–18 versus 0–6 HR = 0.94 (0.91–0.97) 1-point increment
Buckland et al. 2011 (EPIC-Spain) [58]	Spain	1992–1996/ 13.4 (mean)	399/40,622	29–69	CVD (Mortality)	TS, 0–18	HR = 0.66 (0.49–0.89) 11–18 versus 0–6 HR = 0.88 (0.81–0.95) 2-point increment
Chan et al. 2013 [26]	China	2001–2003/ 5.7 (median)	96/1338 M 60/1397 W	≥ 65	Stroke	TS, 0–9	HR = 0.55 (0.31–0.99) 6–9 versus 0–3 HR = 0.72 (0.28–1.87) 6–9 versus 0–3

Table 1 (continued)

First author (study name)	Country	Time recruitment/ Follow-up duration (years)	*N* cases/cohort size or *N* controls	Age at recruitment (years)	Disease (outcome)	MDS, range	Risk estimate (95% confidence interval), highest versus lowest MDS
Dilis et al. 2012 (EPIC-Greece) [17]	Greece	1994–1999/ 10 (median)	636/23,929	20–86	CHD	TS, 0–9	HR = 0.82 (0.66–1.02) 6–9 versus 0–3
							HR = 0.92 (0.84–1.02) 2-point increment
			240/23,689		CHD (Mortality)		HR = 0.54 (0.37–0.81) 6–9 versus 0–3
							HR = 0.78 (0.66–0.92) 2-point increment
			426/9740 M		CHD		HR = 0.9 (0.70–1.16) 6–9 versus 0–3
							HR = 0.98 (0.87–1.10) 2-point increment
			150/9740 M		CHD (Mortality)		HR = 0.62 (0.39–0.98) 6–9 versus 0–3
							HR = 0.81 (0.66–0.99) 2-point increment
			210/9740 W		CHD		HR = 0.62 (0.39–0.99) 6–9 versus 0–3
							HR = 0.85 (0.71–1.02) 2-point increment
			90/9740 W		CHD (Mortality)		HR = 0.39 (0.17–0.88) 6–9 versus 0–3
							HR = 0.75 (0.57–0.98) 2-point increment

Table 1 (continued)

First author (study name)	Country	Time recruitment/ Follow-up duration (years)	*N* cases/cohort size or *N* controls	Age at recruitment (years)	Disease (outcome)	MDS, range	Risk estimate (95% confidence interval), highest versus lowest MDS
Fung et al. 2009[a] (Nurses' Health Study) [46]	USA	1976/ 20	1597/74,886 W	38–63	CHD (incidence)	TS modified, 0–9	HR = 0.78 (0.66–0.93) highest quintile versus lowest
			794/74,886 W		CHD (mortality)		HR = 0.58 (0.45–0.75) highest quintile versus lowest
			959/74,886 W		Ischemic stroke		HR = 0.94 (0.74–1.18) highest quintile versus lowest
			329/74,886 W		Hemorrhagic stroke		HR = 0.79 (0.54–1.16) highest quintile versus lowest
			1480/74,886 W		Stroke (incidence)		HR = 0.90 (0.75–1.08) highest quintile versus lowest
			283/74,886 W		Stroke (mortality)		HR = 0.69 (0.44–1.07) highest quintile versus lowest
Gardner et al. 2011 (Northern Manhattan Study) [59]	USA	1993–2001/ 9 (mean)	518/2568	> 40	CVD	TS, 0–9	HR = 0.80 (0.60–1.06) 6–9 versus 0–2 HR = 0.95 (0.90–1.01) 1-point increment
			171/2568		Ischemic stroke (Incidence)		HR = 1.03 (0.61–1.73) 6–9 versus 0–2 HR = 1.00 (0.90–1.10) 1-point increment
			133/2568		Myocardial infarction (Incidence)		HR = 0.65 (0.38–1.12) 6–9 versus 0–2 HR = 0.94 (0.84–1.05) 1-point increment
George et al. 2014 (Women Health Initiative) [60]	USA	1993–1998/ 12.9 (median)	1483/63,805 W	50–79	CVD (Mortality)	TS modified, 0–9	HR = 0.79 (0.67–0.94) highest quintile versus lowest

Table 1 (continued)

First author (study name)	Country	Time recruitment/ Follow-up duration (years)	*N* cases/cohort size or *N* controls	Age at recruitment (years)	Disease (outcome)	MDS, range	Risk estimate (95% confidence interval), highest versus lowest MDS
Hoevenaar-Blom et al. 2012 (EPIC-The Netherlands) [18]	The Netherlands	1993–1997/ 11.8 (mean)	487/34,708	20–70	CVD (Mortality)	TS, 0–9	HR = 0.44 (0.30–0.66) 7–9 versus 0–2
							HR = 0.78 (0.69–0.88) 2-point increment
			4881/34,708		CVD		HR = 0.84 (0.75–0.96) 7–9 versus 0–2
							HR = 0.95 (0.91–0.98) 2-point increment
			1070/34,708		Myocardial infarction		HR = 0.70 (0.54–0.92) 7–9 versus 0–2
							HR = 0.86 (0.79–0.93) 2-point increment
			379/34,708		Angina pectoris		HR = 1.44 (0.85–2.43) 7–9 versus 0–2
							HR = 1.08 (0.95–1.23) 2-point increment
			154/34,708		Transient ischemic attack		HR = 1.15 (0.58–2.25) 7–9 versus 0–2
							HR = 1.00 (0.81–1.23) 2-point increment
			448/34,708		Stroke		HR = 0.70 (0.47–1.05) 7–9 versus 0–2
							HR = 0.88 (0.78-1) 2-point increment
Knoops et al. 2004 (Survey in Europe on Nutrition and the Elderly: a Concerted Action and Finland Italy Netherlands Elderly study) [61]	Italy, Finland, The Netherlands	1988–1991/10	371/2152	70–90	CVD (Mortality)	TS modified, 0–8	HR = 0.71 (0.58–0.88) ≥ 4 versus 0–3
			122/2152		CHD (Mortality)		HR = 0.61 (0.43–0.88) ≥ 4 versus 0–3
Martinez-Gonzalez et al. 2011 (Seguimento University of Navarra [52])	Spain	1999/4.9 (median)	100/13,609		CVD	TS, 0–9	HR = 0.41 (0.18–0.95) 7–9 versus 0–2
							HR = 0.80 (0.62–1.02) 2-point increment
			68/13,609		CHD		HR = 0.42 (0.16–1.11) 7–9 versus 0–2
							HR = 0.74 (0.55–0.99) 2-point increment

Table 1 (continued)

First author (study name)	Country	Time recruitment/ Follow-up duration (years)	*N* cases/cohort size or *N* controls	Age at recruitment (years)	Disease (outcome)	MDS, range	Risk estimate (95% confidence interval), highest versus lowest MDS
Misirli et al. 2012 (EPIC-Greece) [19]	Greece	1994–1999/10.6 (median)	395/23,601	20–86	Cerebrovascular disease	TS, 0–9	HR = 0.72 (0.54–0.97) 6–9 versus 0–3
							HR = 0.85 (0.74–0.96) 2-point increment
			196/23,601		Cerebrovascular disease (Mortality)		HR = 0.76 (0.50–1.16) 6–9 versus 0–3
							HR = 0.88 (0.73–1.06) 2-point increment
Panagiotakos et al. 2015 (ATTICA study) [62]	Greece	2001–2002/8.41 (median)	299/2583	18–89	CVD	TS modified, 0–55	RR = 0.97 (0.93–1.00) 1-point increment
Reedy et al. 2014 [National Institutes of Health (NIH)–AARP Diet and Health Study] [27]	USA	1995–1996/15	15497/242,321 M	50–71	CVD (Mortality)	TS modified, 0–9	HR = 0.80 (0.76–0.84) 6–9 versus 0–2
			8005/182,342 W	50–71			HR = 0.78 (0.72–0.84) 6–9 versus 0–2
Sjogren et al. 2010 (The Uppsala Longitudinal Study of Adult Men) [63]	Sweden	1970–1974/10.1 (median)	88/924 M	50	CVD (Mortality)	TS modified, 0–8	HR = 0.60 (0.26–1.38) 6–8 versus 0–2
							HR = 0.93 (0.70–1.22) 1-standard deviation increment
Sotos-Preieto et al. 2015 (Health Professionals Follow-up Study and Nurses' Health Study) [23]	USA	1976–1986/20	11793/79,538	30–75	CVD	TS modified, 0–9	HR = 0.93 (0.85–1.02) 5th quintile versus 3rd quintile
			NA		CHD		HR = 0.95 (0.82–1.11) 5th quintile versus 3rd quintile
							HR = 0.98 (0.93–1.02) 20-percentile increment
			NA		Stroke		HR = 0.90 (0.80–1.02) 5th quintile versus 3rd quintile
							HR = 0.93 (0.88–0.98) 20-percentile increment

Table 1 (continued)

First author (study name)	Country	Time recruitment/ Follow-up duration (years)	*N* cases/cohort size or *N* controls	Age at recruitment (years)	Disease (outcome)	MDS, range	Risk estimate (95% confidence interval), highest versus lowest MDS
Tektonidis et al. 2015 (Swedish Mammography Cohort) [21]	Sweden	1998/10.4 (mean)	1109/68,230 W	48–83	Myocardial infarction	TS modified, 0–8	RR = 0.74 (0.61–0.90) highest quartile versus lowest
							RR = 0.92 (0.89–0.96) 1-point increment
			1648/343,381 W		Heart failure		RR = 0.79 (0.68–0.93) highest quartile versus lowest
							RR = 0.94 (0.91–0.97) 1-point increment
			1270/343,408 W		Ischemic stroke		RR = 0.78 (0.65–0.93) highest quartile versus lowest
							RR = 0.94 (0.90–0.98) 1-point increment
			262/347,000 W		Hemorrhagic stroke		RR = 0.88 (0.61–1.29) highest quartile versus lowest
							RR = 0.93 (0.85–1.01) 1-point increment
Tognon et al. 2012 (Vasterbotten Intervention Program) [64]	Sweden	1985/18	680/73,984	30–70	CVD (Mortality)	TS modified, 0–8	HR = 0.96 (0.92–1.01) 1-point increment
			305/73,984		Myocardial infarction (Mortality)		HR = 0.94 (0.87–1.01) 1-point increment
			144/73,984		Stroke (Mortality)		HR = 0.99 (0.89–1.09) 1-point increment
Tognon et al. 2014 (MONItoring of trends and determinants in CArdiovascular disease -Danish) [65]	Denmark	1982–1983/11	755/1849		CVD	TS modified, 0–8	HR = 0.94 (0.89–0.99) 1-point increment
			223/1849		CVD (Mortality)		HR = 0.90 (0.82–0.99) 1-point increment
			161/1849		Myocardial infarction		HR = 0.89 (0.8–1.00) 1-point increment
			64/1849		Myocardial infarction (Mortality)		HR = 0.80 (0.67–0.96) 1-point increment
			167/1849		Stroke		HR = 0.96 (0.86–1.07) 1-point increment
			40/1849		Stroke (Mortality)		HR = 1.03 (0.82–1.3) 1-point increment

Table 1 (continued)

First author (study name)	Country	Time recruitment/ Follow-up duration (years)	*N* cases/cohort size or *N* controls	Age at recruitment (years)	Disease (outcome)	MDS, range	Risk estimate (95% confidence interval), highest versus lowest MDS
Tong et al. 2016[b] (EPIC-Norfolk) [66]	UK	1993–1997/12.2 (mean)	7606/23,902	40–79	CVD	TS, 0–9	HR = 0.97 (0.92–1.03) 6–9 versus 0–3
					CVD		HR = 0.98 (0.96–1.01) 1 SD increment
			1714/23,902		CVD (Mortality)		HR = 0.94 (0.89–0.98) 1 SD increment
			2967/23,902		IHD		HR = 0.97 (0.93–1.01) 1 SD increment
			817/23,902		IHD (Mortality)		HR = 0.91 (0.84–0.97) 1 SD increment
					Stroke		
			1023/23,902		Stroke (Mortality)		HR = 0.96 (0.94–1.01) 1 SD increment
			509/23,902				HR = 0.98 (0.90–1.08) 1 SD increment
Trichopoulou et al. 1995 [67]	Greece	1988–1990/6	53/182	> 70	CVD (Mortality)	TS modified, 0–8	RR = 0.83 (0.69–0.99) 1-point increment
Tsivgoulis et al. 2015 (REasons for Geographic and Racial Differences in Stroke) [20]	USA	2003–2007/6.5 (mean)	497/20,197	≥ 45	Ischemic stroke	TS, 0–9	HR = 0.78 (0.60–1.01) 6–9 versus 0–3
							HR = 0.91 (0.78–1.05) 1-point increment
			68/20,197		Hemorrhagic stroke		HR = 1.58 (0.83–2.99) 6–9 versus 0–3
Case–control studies							
Georgousopoulou et al. 2014 (population based) [47]	Greece	2009–2010	250/250		CHD (Incidence)	TS modified, 0–55	OR = 0.92 (0.87–0.98) 1-point increment
					Ischemic stroke (Incidence)		OR = 0.91 (0.84–0.98) 1-point increment
Martinez-Gonzalez et al. 2002 (hospital based) [50]	Spain	1999–2001	171/171	< 80	Myocardial infarction (Incidence)	TS modified, 5–40	OR = 0.21 (0.06–0.73) > 30 versus < 20
							OR = 0.92 (0.86–0.98) 1-point increment
Panagiotakos et al. 2005 (population based) [68]	Greece	2000–2001	848/1078	All ages	CHD (Incidence)	TS modified, 0–55	OR = 0.73 (0.66–0.89) 10-point increment
Turati et al. 2015 (hospital based) [69]	Italy	1995–2003	760/682	16–79	Myocardial infarction (Incidence)	TS, 0–9	OR = 0.55 (0.40–0.75) 6–9 versus 0–4
							OR = 0.91 (0.85–0.98) 1-point increment

Table 1 (continued)

First author (study name)	Country	Time recruitment/ Follow-up duration (years)	*N* cases/cohort size or *N* controls	Age at recruitment (years)	Disease (outcome)	MDS, range	Risk estimate (95% confidence interval), highest versus lowest MDS
Yau et al. 2011 (hospital and population based) [34]	Australia	2008	44/46	23–92	Stroke (Incidence)	TS modified, 0–20	OR = 0.12 (0.03–0.44) ≥ versus < median score of the controls

M men, *W* women, *CHD* coronary heart disease, *CVD* cardiovascular disease, *IHD* ischemic heart disease, *MDS* Mediterranean diet score, *OR* odds ratio, *HR* hazard ratio, *TS* Trichopoulou score [1], *EPIC* European prospective investigation into cancer and nutrition, *NA* not applicable, *SD* standard deviation

[a]The study was included only for stratified analyses

[b]Among proposed score we reported MDS tertiles

The pooled RR for the six studies that considered unspecified stroke was 0.73 (95% CI 0.59–0.91) for the highest versus the lowest category of the MDS (Fig. 3), with a significant inverse relationship across strata of study design (RR 0.77 for cohort studies and 0.12 for the single case–control study, p for heterogeneity = 0.05), sex (RR 0.83 for women and 0.70 for men), and geographic area (RR 0.76 for Mediterranean and 0.66 for non-Mediterranean countries), and the MDS used (RR 0.74, 95% CI 0.62–0.89, for TS, and 0.36, 95% CI 0.05–2.41, for the two studies using alternative scores, p for heterogeneity = 0.85) (Table 2). The inverse association was significant for the two studies evaluating mortality (RR 0.73, 95% CI 0.53–0.99), but not for the two studies evaluating incidence (RR 0.37, 95% CI 0.05–2.62), in the absence of a significant heterogeneity across the strata (p for heterogeneity = 0.63). The relationship of the MD with ischemic and hemorrhagic stroke was considered in five and four studies, respectively, resulting in a pooled RR for the highest versus the lowest MDS of 0.82 (95% CI 0.73–0.92) for ischemic and 1.01 (95% CI 0.74–1.37) for hemorrhagic stroke (p for heterogeneity = 0.31, Fig. 3; Table 2).

The pooled RR for the highest versus the lowest category of the MDS was 0.81 (95% CI 0.74–0.88) based on the 11 studies that considered unspecified CVD (Fig. 4). The inverse relationship was consistent across strata of sex and MDS used. The inverse relationship was also consistent among strata of the other considered covariates with an overall RR of 0.61 (95% CI 0.44–0.86) for the two studies conducted in Mediterranean areas and 0.84 (95% CI 0.77–0.92) for the eight conducted in non-Mediterranean areas (p for heterogeneity = 0.11).

The Begg's and Egger's tests were, respectively, 0.087 and 0.034 for CHD/AMI, 0.13 and 0.008 for unspecified stroke, and 0.44 and 0.27 for unspecified CVD, showing a potential for publication bias for CHD/AMI and unspecified stroke.

In the sensitivity analysis, excluding one study at a time, the RRs for the highest versus the lowest category of MDS ranged from 0.68 (95% CI 0.60–0.77) to 0.72 (95% CI 0.64–0.82) for CHD/AMI, from 0.69 (95% CI 0.52–0.90) to 0.77 (95% CI 0.67–0.90) for unspecified stroke, and from 0.79 (95% CI 0.72–0.87) to 0.82 (95% CI 0.75–0.89) for unspecified CVD.

In the studies using the TS, we estimated the effect of an increment of one point of the MDS, which approximately corresponds to the addition of one favorable dietary habit. The RRs were 0.95 (95% CI 0.92–0.99) for CHD/AMI (six studies), 0.95 (95% CI 0.92–0.98) for unspecified stroke (five studies), and 0.97 (95% CI 0.96–0.99) for unspecified CVD (four studies).

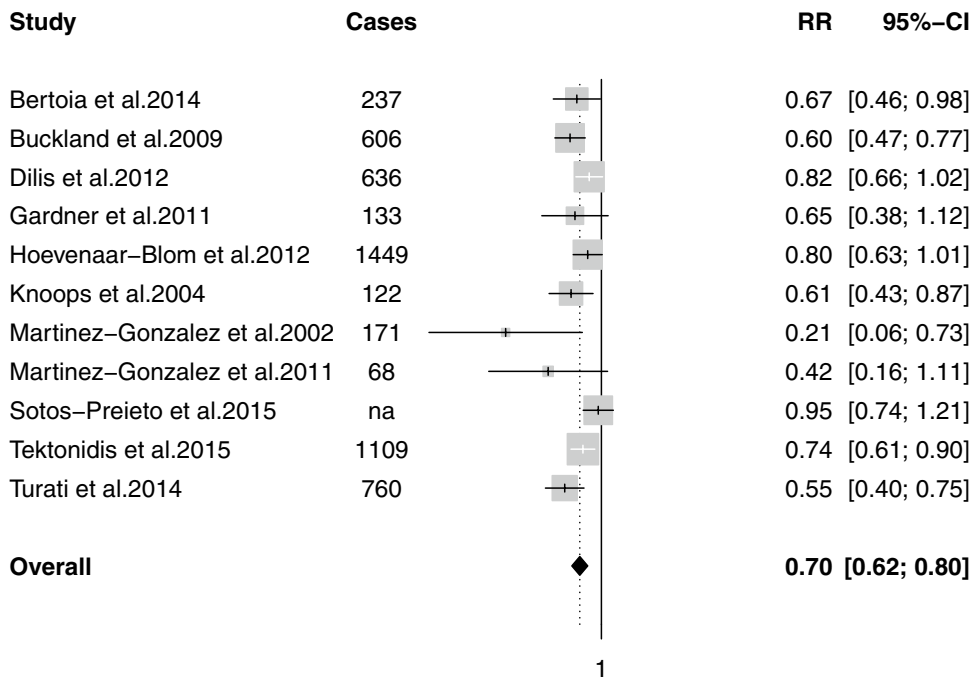

Fig. 2 Summary relative risk of coronary/ischemic heart disease and acute myocardial infarction for the highest versus the lowest category of Mediterranean diet score

Discussion

This meta-analysis, based on 29 publications (corresponding to 26 studies), shows a favorable role of the MD on CVD, with a decreased risk of about 20–25% for subjects with the highest adherence compared to those with the lowest one. The inverse relationship was consistent across strata of sex, study design, and type of the MDS used, and for different types of CVD (CHD/AMI, ischemic stroke), but no association was found with hemorrhagic stroke. The risk of CVD was 3% lower for an increment of one component of the MD when studies using the TS were pooled, indicating a dose–risk relationship. The existence of a real inverse association is further supported by the consistent results across studies, as the exclusion of any study from the analysis did not materially change the summary estimates.

Although based on a few studies, the finding of a lack of association for hemorrhagic stroke has no clear explanation. Both ischemic and hemorrhagic stroke have been associated with an unhealthy diet, but the relationship of cholesterol and lipoprotein profiles with ischemic and hemorrhagic stroke are different [70] and deserves further investigations.

We found stronger associations in case–control studies than in cohort ones, which reflects an exposure assessment closer to the disease onset in the former. However, the number of case–controls studies included is small. Although not significant, stronger associations were found for CHD/AMI in studies conducted in countries with a tradition of MD than in those without such tradition. This likely depends, at least in part, on the definition of the a priori MDS and of the prevalence of Mediterranean diet habits in various populations [1, 2, 67]. The cut points for components of the MD used for assessing a subject's adherence to the MD are study specific, as they are defined on the basis of the distribution of consumption of each selected food in the population of controls and not in absolute terms (i.e., actual quantity of each food). Consequently, subjects with a higher MDS who live in Mediterranean countries generally have a higher absolute intake of Mediterranean food components than do populations living elsewhere.

The consistent relationship across sex and other subgroup analyses further support a real inverse association. Moreover, our findings are broadly consistent with those from other meta-analyses, including the two most recent ones [5, 13], but add information, mainly regarding the different effect of MD on ischemic and hemorrhagic stroke. There is only weak supporting evidence from randomized controlled trials, as none has compared CVD risk between subjects who follow a MD and those who do not. The PREDIMED trial studied the addition of either olive oil or nuts to the diet of a Spanish population, which presumably has a diet close to the MD, and demonstrated that CVD can be reduced by approximately 30% by an increased intake of either olive oil, especially extra-virgin olive oil, or nuts [71]. For unspecified stroke and unspecified CVD, only two studies were conducted in Mediterranean countries, thus the estimates are only indicative and the issue requires further investigation.

Our analyses have several strengths. First, compared with previous meta-analyses we included case–control studies and more cohort studies. Second, we stratified for many variables, including outcome (CHD/AMI or ischemic/hemorrhagic stroke), end point, sex, geographic

Table 2 Summary relative risks (RRs) of coronary heart disease, stroke, and cardiovascular disease, and 95% confidence intervals (CIs), for the highest versus the lowest Mediterranean diet score (MDS) category

	No. studies	RR (95% CI)[a]	Heterogeneity between study, I^2, p[b]	Heterogeneity across strata[c]
CHD/AMI	11	0.70 (0.62–0.80)	44.5%, 0.06	
Study design				
Cohort	9	0.74 (0.66–0.83)	26.5%, 0.21	0.09
Case–control	2	0.41 (0.18–0.98)	53.4%, 0.14	
Endpoint				
Incidence	4	0.62 (0.46–0.85)	59.6%, 0.06	0.43
Mortality	4	0.59 (0.50–0.70)	0%, 0.88	
Sex				
Women	6	0.70 (0.64–0.78)	0%, 0.92	0.93
Men	3	0.67 (0.49–0.93)	71.6%, 0.029	
Geographic area[d]				
Mediterranean	5	0.61 (0.46–0.79)	59.0%, 0.045	0.17
Non-Mediterranean	5	0.79 (0.70–0.89)	0%, 0.43	
Mediterranean Diet Score				
Trichopoulou 2003	6	0.68 (0.58–0.81)	38.7%, 0.15	0.63
Alternative score	5	0.72 (0.57–0.90)	56.3%, 0.06	
Stroke	6	0.73 (0.59–0.91)	46.1%, 0.10	
Type				
Ischemic	5	0.82 (0.73–0.92)	0%, 0.46	0.31
Hemorrhagic	4	1.01 (0.74–1.37)	35.6%, 0.20	
Study design				
Cohort	5	0.77 (0.67–0.90)	0%, 0.74	0.05
Case–control	1	0.12 (0.03–0.46)	–	
End point				
Incidence	2	0.37 (0.05–2.62)	88.2%, 0.004	0.63
Mortality	2	0.73 (0.53–0.99)	0%, 0.76	
Sex				
Women	3	0.83 (0.71–0.97)	0%, 0.37	0.57
Men	2	0.70 (0.51–0.97)	0%, 0.33	
Geographic area				
Mediterranean	2	0.76 (0.60–0.95)	0%, 0.59	0.99
Non-Mediterranean	4	0.66 (0.45–0.97)	66.6%, 0.030	
Mediterranean Diet Score				
Trichopoulou 2003	4	0.74 (0.62–0.89)	0%, 0.74	0.85
Alternative score	2	0.36 (0.05–2.41)	87.3%, 0.005	
CVD	11	0.81 (0.74–0.88)	79.9%, <0.001	
Study design				
Cohort	11	0.81 (0.74–0.88)	79.9%, <0.001	–
Case–control	0	–	–	
End point				
Incidence	0	–	–	–
Mortality	7	0.73 (0.67–0.81)	47.1%, 0.08	
Sex				
Women	3	0.85 (0.72–0.99)	86.0%, 0.001	0.98
Men	3	0.85 (0.74–0.98)	78.6%, 0.009	
Geographic area[d]				
Mediterranean	2	0.61 (0.44–0.86)	10.3%, 0.29	0.11
Non-Mediterranean	8	0.84 (0.77–0.92)	83.1%, <0.001	

Table 2 (continued)

	No. studies	RR (95% CI)[a]	Heterogeneity between study, I^2, p[b]	Heterogeneity across strata[c]
Mediterranean Diet Score				
Trichopoulou 2003	5	0.82 (0.70–0.97)	72.6%, 0.006	0.52
Alternative score	6	0.80 (0.73–0.87)	65.8%, 0.012	

CHD coronary/ischemic heart disease, *AMI* acute myocardial infarction, *CVD* cardiovascular disease

[a]The summary RR estimates were calculated using the random-effects models. The reference was the lowest adherence to the MDS category

[b]p value for heterogeneity within each subgroup. I^2 is interpreted as the proportion of total variation across studies due to heterogeneity rather than chance

[c]p value for heterogeneity across subgroups with meta-regression analysis

[d]Knopps et al. 2004 [61] is not included in this stratified analysis as it was conducted in both Mediterranean and non-Mediterranean countries

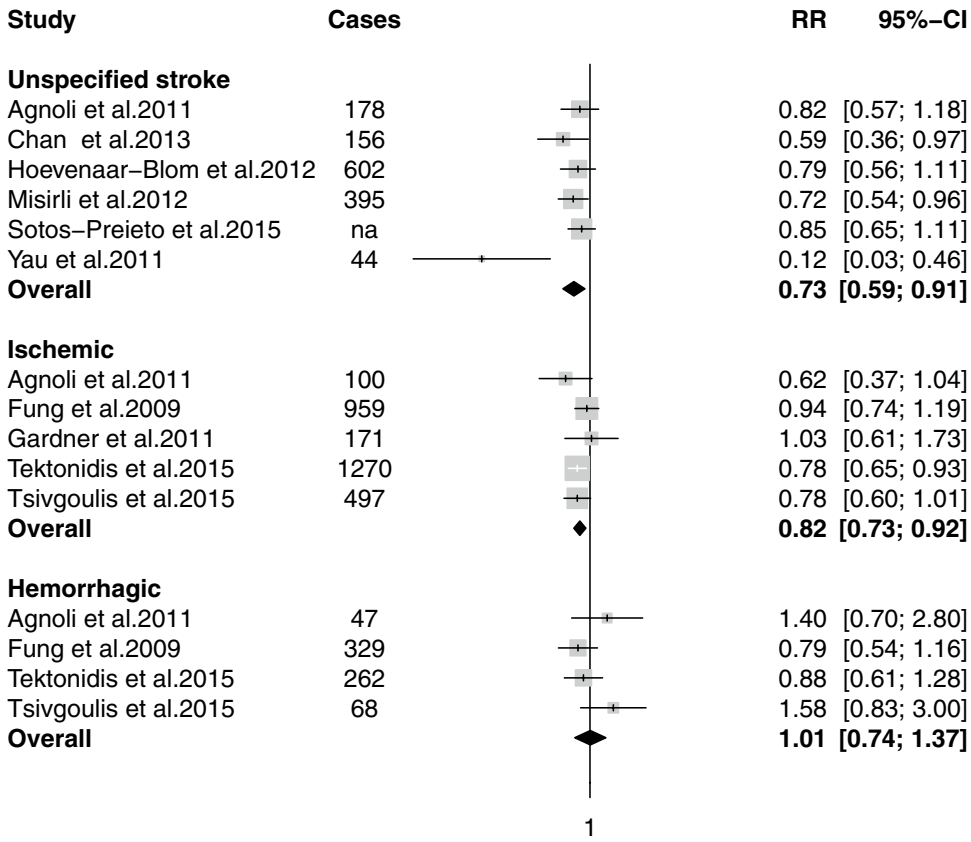

Fig. 3 Summary relative risks of stroke for the highest versus the lowest category of Mediterranean Diet Score

region (Mediterranean/non-Mediterranean countries), study design and type of MDS. Third, we used a priori criteria for the inclusion of original studies. In addition, we excluded cross-sectional studies and randomized clinical trials [15]. Moreover, we have performed a meta-regression analysis to compare results taking incidence and mortality as end points, and when a paper reported both we have used only the wider category of incidence to avoid overlapping (inclusion of cases twice).

As for limitations, with reference to confounding, all original papers included in this meta-analysis, except one [67] were published after 2000, and the risk estimates had been adjusted for main confounding factors for CVD and diet. A limitation is the use of different definitions of MD in terms of different categorizations of the scores, inclusion of different foods and/or with different cut points. As an example, much research indicates that some foods that are highly consumed in the MD provide significant protection against

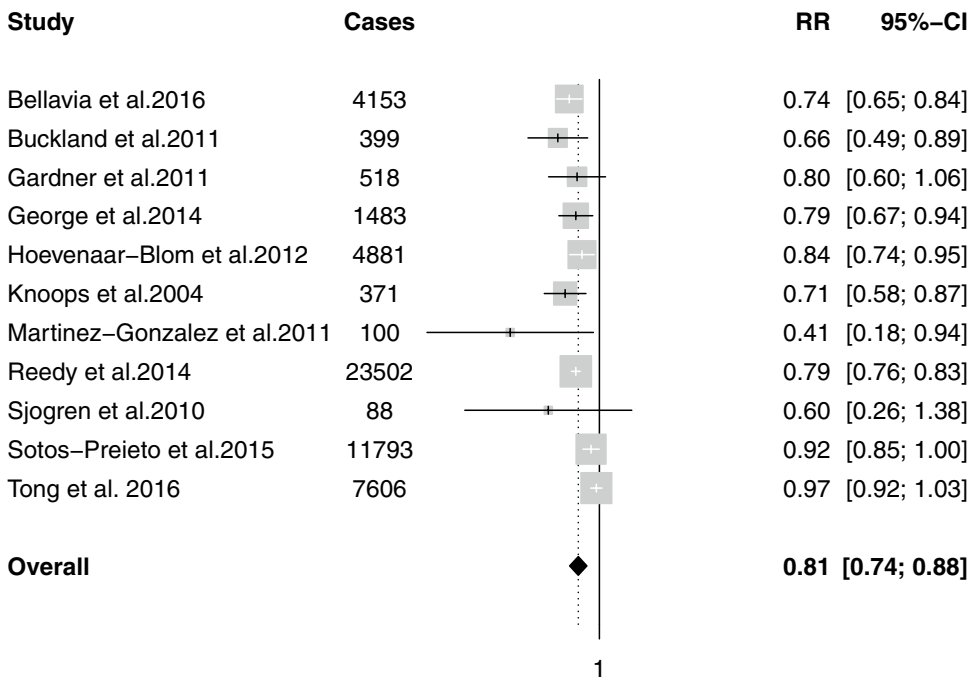

Fig. 4 Summary relative risks of unspecified cardiovascular disease for the highest versus the lowest category of Mediterranean Diet Score

CVD, whereas other components provide little or no protection. In particular, there is strong evidence that the following components of the MD provide significant protection against CVD: olive oil [72, 73], fruit, vegetables, legumes, nuts, and a higher consumption of fish compared with meat and meat products [74]. Alcoholic beverages, including wine, are also protective against CVD when consumed in moderation [75, 76]. A problematic component of the MD is a high consumption of grains and cereals, which are the main source of energy. However, while much evidence indicates that whole grains are protective against CVD, refined grains are not protective and may actually induce an increased risk [74]. Compounding this problem, some cohort studies have based their scoring system on the total intake of grains whereas others have only considered whole grains. Similarly, some studies included potatoes among vegetables while others did not.

Another limitation is that the asymmetry in the funnel plot and significant p values from Begg's and Egger's tests indicate that our results for CHD/AMI and strokes can be influenced by publication bias. However, when we stratified studies by the number of cases of CHD/AMI, we found a RR for the highest versus the lowest MDS of 0.71 (95% CI 0.64–0.79) and 0.60 (95% CI 0.48–0.76), respectively, for studies including more than 600 cases compared with smaller studies. Similarly, for unspecified stroke, the RRs were 0.82 (95% CI 0.72–0.94) and 0.52 (95% CI 0.26–1.03) for studies including more than 300 cases compared with smaller studies. This lack of material difference by study size further indicates that publication bias should not materially influence our findings. Moreover, the sensitivity analysis shows that the exclusion in turn of each paper did not materially change the pooled risk estimate, suggesting that no one paper is materially responsible for the inverse association.

The protective effect of the Mediterranean diet on vascular disease is plausible. In terms of nutrients, the MD is low in saturated fatty acids, rich in monounsaturated fatty acids, especially oleic acid, (mainly from olive oil), high in complex carbohydrates (from cereals and legumes) and high in fiber (from vegetables, fruit, cereals and legumes). Moreover, the high content of vegetables, fresh fruits, cereals and olive oil implies a high consumption of folate, flavonoids, polyphenols, vitamins C and E, and of various minerals, such as potassium and magnesium. These nutrients have favorable effects on cardiovascular health [74]. However, most of the beneficial effect is evident mostly when considering the whole MD rather than single components. This may depend on several factors, such as that the benefit of each component is too small to be detected, or that the effect of each component is synergistic with that of the others.

MD causes small favorable changes in most risk factors, including metabolic syndrome [9, 77–79], and its components, such as total blood cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, blood pressure [80], blood glucose [81], and waist circumference. Moreover, the MD has been related to many biochemical parameters related to CV health. Observational studies have shown that MD is related to lower endothelial dysfunction and favorable plasma concentrations of biomarkers [82], less carotid atherosclerosis [83], elevated non-enzymatic total antioxidant capacity and low oxidized LDL-cholesterol concentrations [84], lower

insulin resistance [85], and selective measures of cardioprotective lipid profiles, glucose metabolism, and inflammation and coagulation levels [86].

In conclusion, compared with previously available analyses, our findings reinforce and more precisely quantify the protective association between consumption of the MD and the risk of CVD. Our findings add significant new information by demonstrating that this protective effect includes CHD and ischemic stroke but not hemorrhagic stroke.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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