

Florence “Sustainability of Well-Being International Forum”. 2015: Food for Sustainability and not just food, FlorenceSWIF2015

Eating the Mediterranean Style: a Tasty Way for Stroke Prevention

Antonio Di Carlo^{a*}, Marzia Baldereschi^a, Domenico Inzitari^b

^a*Institute of Neuroscience, Italian National Research Council, Florence, Italy;*

^b*Department of Neurofarba, Neuroscience Section, University of Florence, Florence, Italy.*

Abstract

Stroke is a leading cause of death and disability, with high individual, social and economic costs. Diet has been identified as a modifiable risk factor for cardiovascular diseases and stroke in several large epidemiological studies. The evaluation of foods groups and dietary patterns provides a more realistic representation of actual dietary intake, and gives clues to developing guidelines aimed at general population. We review the role of Mediterranean diet, fruit and vegetables, and olive oil consumption, on the risk of stroke and other vascular outcomes. Findings from major studies indicate that, together with a healthy lifestyle, the traditional Mediterranean way of eating, including social and cultural components, and inscribed on the Representative List of the Intangible Cultural Heritage of Humanity by UNESCO, may be considered a cost-effective intervention to reduce the human, social and economic burden of stroke and cardiovascular disease.

© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Peer-review under responsibility of Fondazione Simone Cesaretti

Keywords: Stroke; Mediterranean Diet; Cardiovascular Prevention.

1. Introduction

Stroke is a leading cause of death and disability, with about 16 million events occurring annually in the world, causing a total of 5.7 million deaths (Strong et al., 2007). As a consequence, stroke ranks as the second cause of death in the world population after ischaemic heart disease (the third only if neoplastic diseases are considered as a group) (Di Carlo, 2009).

* Corresponding author. Phone +39 055 5225032 - Fax +39 055 5225035.

E-mail address: dicarlo@in.cnr.it

Stroke is also a costly disease. In western countries, on average, 0.27% of gross domestic product is spent on stroke by national health systems, and stroke care accounts for about 3% of total health care expenditures (Evers et al., 2004). In the 27 EU countries, total annual cost of stroke is estimated at €27.2 billion, €9.1 billion (70.2%) for direct and €8.1 billion (29.8%) for indirect costs. A further sum of €1.1 billion is calculated for the value of informal care (Nichols et al., 2012).

Italy is one of the countries with the most rapidly increasing percentages of elderly population, a prevalence of stroke in people aged over 65 years of 6.5%, and about 200,000 new stroke cases expected each year (Di Carlo et al., 2003).

Given the significant impact on public health, the identification of possible modifiable risk factors is essential to reduce the burden of this condition. In particular, diet has been identified as a modifiable risk factor for stroke in several large epidemiological studies, and the evaluation of population attributable risk indicates that we can achieve a significant reduction in incidence through generalized prevention campaigns aimed at education to healthy lifestyle (Boden-Albala and Sacco, 2000; O'Donnell et al., 2010; Agnoli et al., 2011; Tikk et al., 2014).

In past decades, clinical research in nutrition and its relation with diseases was centered on micro- or macro-nutrients, such as vitamins, while more recently a growing body of evidence focused on the relevance of foods groups (e.g., fruits), or dietary patterns and their role on the incidence of cardiovascular diseases and stroke (Dearborn et al., 2015). Dietary patterns are more realistic representations of actual dietary intake, and are also useful for developing guidelines for the general population (Agnoli et al., 2011), as they are closer to behaviours that can be modified than nutrient intakes (Hulshof et al., 2001).

We will review main evidences on the links between nutrition and cerebrovascular disease, focusing on fruit and vegetables, and olive oil, considered in light of their role as components of the Mediterranean diet.

2. Fruit and vegetables consumption and stroke risk

In 2005, the World Health Organization evaluated the total worldwide mortality attributable to inadequate consumption of fruit and vegetables to be up to 2.64 million deaths per year. Increasing individual fruit and vegetable consumption up to 600 g per day (the baseline of choice) could reduce the burden of ischemic heart disease and stroke by 31% and 19%, respectively (Lock et al. 2005).

The role of fruit and vegetables consumption on the risk of stroke was evaluated in a series of cohort studies.

The Finnish Mobile Clinic Health Examination Survey evaluated the relationship between consumption of plant foods (i.e. fruits and berries, vegetables, and cereals) and incidence of cerebrovascular disease in a population with low fruit and vegetable and high wholegrain intake. A cohort of 3,932 men and women, aged 40-74 years and free of cardiovascular diseases at baseline, was followed for 24 years. An inverse association was found between fruit consumption and the incidence of cerebrovascular diseases, ischemic stroke and intracerebral hemorrhage, with a risk reduction of 25%, 27% and 53%, respectively. These associations were primarily due to the consumption of citrus fruits and cruciferous vegetables (Mizrahi et al. 2009).

In the Japan Collaborative Cohort Study for Evaluation of Cancer Risk, 25,206 men and 34,279 women aged 40-79 years were followed for 13 years. Fruit intake in the highest versus the lowest quartiles was inversely associated with vascular mortality, mortality from stroke (33% risk reduction), and total mortality (Nagura et al., 2009).

In a prospective study in Sweden on 74,961 participants free from stroke, coronary heart disease, and cancer at baseline, followed for a mean of 10.2 years, a comparison of the highest versus the lowest category of total fruit and vegetable consumption showed a multivariable relative risk reduction for total stroke of 13% (Larsson et al., 2013).

The associations between food group consumption and risk of death from stroke among ethnic groups in the United States was evaluated in the US Multiethnic Cohort Study, including >215,000 participants of 5 ethnic groups: African Americans, Native Hawaiians, Japanese Americans, Latinos, and Caucasians. Vegetable intake was associated with a significant reduction in risk for fatal stroke among African American women. Among Japanese American women only, high fruit intake was significantly associated with a risk reduction for stroke mortality. Among men, a significant reduction in stroke mortality was observed among Native Hawaiians (Sharma et al., 2013).

The Swedish Mammography Cohort and the Cohort of Swedish Men included 69,677 participants aged 45-83 years, followed for 10.3 years. High intakes of total fiber and fiber from fruits and vegetables but not from cereals

were inversely associated with risk of stroke. After adjustment for other risk factors, comparing the highest versus the lowest quintile of intake, a risk reduction of 10% for total fiber and vegetable fiber, and 15% for fruit fiber was found for total stroke incidence (Larsson and Wolk, 2014).

Two meta-analyses evaluated the relation between fruit and vegetable intake and incidence of stroke in cohort studies.

The first one considered 8 studies, including 257,551 individuals (4,917 stroke events) with an average follow-up of 13 years. Compared with individuals who had less than three servings of fruit and vegetables per day, the pooled relative risk of stroke was 0.89 (95% CI 0.83-0.97) for those with three to five servings per day, and 0.74 (95% CI, 0.69-0.79) for those with more than five servings per day. Fruit and vegetables showed a significant protective effect on both ischemic and hemorrhagic stroke in subgroup analyses (He et al., 2006).

The more recent meta-analysis included 20 prospective cohort studies, 760,629 participants and 16,981 stroke events. The multivariable relative risk of stroke for the highest versus lowest category of total fruits and vegetables consumption was 0.79 (95% CI, 0.75-0.84). The relative risk was 0.77 (95% CI, 0.71-0.84) for fruits consumption, and 0.86 (95% CI, 0.79-0.93) for vegetables consumption. Citrus fruits, apples/pears, and leafy vegetables seemed those more contributing to the protection. Every 200 g per day increment in fruits and vegetables consumption decreased the risk of stroke by 32% and 11%, respectively (Hu et al., 2014).

3. Olive oil consumption and stroke risk

Oleic acid is a monounsaturated fatty acid (MUFA), and represents about 90% of all MUFA provided in the diet. According to the European Prospective Investigation into Cancer and Nutrition (EPIC), performed in 27 centers across 10 countries, extra virgin olive oil was the most dominant source of this type of fatty acid in Italy, Greece, and Spain, whereas in most other EPIC centers the main contributors to total MUFA intake were meat and meat products, added fats and dairy products (Linseisen et al., 2009). High consumption of olive oil is among main characteristics of the Mediterranean diet, and is considered a major contributor to its protective effect on the cardiovascular system (López-Miranda et al., 2010).

In the Greek arm of the EPIC Study, intakes of olive oil, vegetables, and fruit were significantly and inversely associated with both systolic and diastolic blood pressure, with a dominant beneficial effect of olive oil (Psaltopoulou et al. 2004). In the Spanish population of the EPIC Study, including 40,622 participants aged 29-69 years, in comparison with non-consumers, the highest quartile of olive oil consumption was associated with a 26% reduction in risk of overall mortality and a 44% reduction in risk of cardiovascular mortality (Buckland et al., 2012).

The possible protective effect of olive oil on the risk of incident stroke was evaluated among participants from the Three-City (Bordeaux, Dijon and Montpellier) Study with no history of stroke at baseline, in a main sample of 7,625 subjects for olive oil consumption and in a secondary sample of 1,245 subjects for plasma oleic acid. The median follow-up was 5.25 years. Intensive use of olive oil was linked to a 41% lower risk of stroke. In the secondary sample, higher plasma oleic acid was associated with lower stroke incidence. Compared to those in the first tertile, participants in the third tertile of plasma oleic acid had a 73% reduction of stroke risk (Samieri et al., 2011).

In the cohort of 23,601 participants from the Greek segment of the EPIC Study free of cardiovascular diseases and cancer at baseline, during a median follow-up period of 10.6 years, a 23 g/day increment in consumption of olive oil was inversely associated with stroke incidence (20% risk reduction) and mortality (11% risk reduction) (Misirli et al., 2012).

In a meta-analysis of 32 cohort studies including 841,211 subjects, the comparison of the top versus bottom third of the distribution of a combination of MUFA (of both plant and animal origin), olive oil, oleic acid, and MUFA/saturated fatty acids ratio resulted in a significant risk reduction for all-cause mortality, cardiovascular mortality, cardiovascular events, and stroke. In particular, the risk for incident stroke was reduced by 17% considering all MUFA combined, and by 40% considering only olive oil intake (Schwingshackl and Hoffman, 2014).

4. Towards a synthesis: Mediterranean diet and stroke risk

Mediterranean diet is among dietary patterns most often considered for a possible impact on stroke burden in the general population. The traditional Mediterranean diet is characterized by olive oil as the principal source of fat, a high intake of fruit, nuts, vegetables, legumes and cereals; a moderate intake of fish and poultry; a low intake of dairy products, red meat, processed meats, and sweets; and wine consumed in low to moderate amounts, usually with meals (Willett et al., 1995).

Adherence to Mediterranean diet was found to reduce the risk of hypertension (Psaltopoulou et al. 2004), diabetes (Martínez-González et al. 2008), coronary heart disease (Buckland et al., 2009), obesity (Buckland et al., 2008), and metabolic syndrome (Salas-Salvadó J et al., 2008). A meta-analysis of prospective studies, including a total of 2,190,627 subjects, showed that a 2-point increase in adherence to the Mediterranean diet was associated with a significant reduction of overall mortality, cardiovascular incidence or mortality, cancer incidence or mortality, and incidence of neurodegenerative diseases (Sofi et al., 2010). In a meta-analysis of randomized controlled trials comparing Mediterranean to low-fat diets, individuals assigned to a Mediterranean diet had more favorable changes in weighted mean differences of body weight, body mass index, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, and high-sensitivity C-reactive protein (Nordmann et al., 2011).

The specific role of Mediterranean diet on cardiovascular and stroke risk has been evaluated in cohort studies and in primary prevention trials inside and outside the Mediterranean basin (Table 1).

Table 1. Mediterranean diet and risk of stroke and other vascular events in longitudinal studies.

Author, year	Study	No. participants	Years of follow-up	Comparison	Outcome	Relative risk (95% CI)
Fung et al., 2009 ³⁴	Nurses' Health Study	74,886	20	Top vs. bottom quintile of alternate Mediterranean diet score	Coronary heart disease	0.71 (0.62-0.82)
					Fatal coronary heart disease	0.58 (0.45-0.75)
					Stroke	0.87 (0.73-1.02)
					Fatal stroke	0.69 (0.44-1.07)
					Vascular death	0.61 (0.49-0.76)
Gardener et al., 2011 ³⁵	Northern Manhattan Study	2,568	9	Top vs. bottom quintile of Mediterranean diet score	Combined ischemic stroke, myocardial infarction and vascular death	0.75 (0.56-0.99)
Agnoli et al., 2011 ⁸	EPICOR	40,681	7.9	Highest vs. lowest tertile on the Italian Mediterranean Index	All stroke	0.47 (0.30-0.75)
					Ischemic stroke	0.37 (0.19-0.70)
					Hemorrhagic stroke	0.51 (0.22-1.20)
Hoeveraar-Bloom et al., 2012 ³⁶	EPIC-NL Cohort study	34,708	12	2-unit increment in Mediterranean diet score	Total cardiovascular disease	0.95 (0.91-0.98)
					Fatal cardiovascular disease	0.78 (0.69-0.88)
					Myocardial infarction	0.86 (0.79-0.93)
					Stroke	0.88 (0.78-1.00)
Estruch et al., 2013 ³⁷	PREDIMED Study	7,447	4.8	Mediterranean diet supplemented with extra-virgin olive oil or nuts vs. control group	Myocardial infarction, stroke or vascular death	0.70 (0.54-0.92) (olive oil) 0.72 (0.54-0.96) (nuts)
					Stroke	0.67 (0.46-0.98) (olive oil) 0.54 (0.35-0.84) (nuts)

In the Nurses' Health Study, a total of 74,886 women aged 38-63 years, without a history of cardiovascular disease, were followed for two decades. A greater adherence to the Mediterranean diet was associated with a 29% and 13% lower risk of incident coronary heart disease and stroke, respectively (Fung et al., 2009).

In 2,568 participants in the Northern Manhattan Study, increased adherence to Mediterranean diet over a mean follow-up of 9 years was inversely associated with a 25% reduction of the composite outcome of ischemic stroke, myocardial infarction or vascular death (Gardener et al., 2011).

The EPICOR study evaluated the association between stroke and adherence to different dietary patterns (Agnoli et al., 2011). An Italian Mediterranean Index adapted the Greek Mediterranean Index to Italian eating behavior, and was based on intake of 11 items: high intakes of 6 typical Mediterranean foods (pasta; typical Mediterranean vegetables such as raw tomatoes, leafy vegetables, onion, and garlic, salad, and fruiting vegetables; fruit; legumes; olive oil; and fish); low intakes of 4 non-Mediterranean foods (soft drinks, butter, red meat, and potatoes); and also alcohol. A total of 40,681 volunteers were followed for a mean follow-up of 7.9 years. A diet with a high score on the Italian Index was associated with the greatest risk reduction of incidence of all types of stroke (53%), ischemic (63%) and hemorrhagic stroke (49%).

In the EPIC-NL Study, a cohort of 34,708 participants free of cardiovascular disease at baseline were followed for 12 years. A 2-unit increment in the Mediterranean Diet Score was inversely associated with incidence of fatal and total cardiovascular disease, stroke (12% risk reduction), myocardial infarction and pulmonary embolism (Hoevenaer-Blom et al., 2012).

The PREDIMED study was a multicenter Spanish trial which enrolled 7,447 persons (aged 55-80 years) at high cardiovascular risk, but with no cardiovascular disease at enrollment. Participants were randomly assigned to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat). The primary end point was the rate of major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes). The trial was stopped on the basis of the results of an interim analysis, after a median follow-up of 4.8 years. Main findings were a 28% reduction of major cardiovascular events for the group assigned to a Mediterranean diet with nuts and a 30% reduction for the group assigned to a Mediterranean diet with extra-virgin olive oil, compared with the control group. Regarding components of the primary end point, only the comparisons of stroke risk, with a 33% (olive oil) and 46% (nuts) reduction, reached statistical significance (Estruch et al., 2013).

A meta-analysis evaluated the association between adherence to a Mediterranean diet and risk of stroke, depression, and cognitive impairment. Eleven studies covered stroke, and included 162,092 subjects. High adherence to Mediterranean diet was associated with a 29% reduced risk for stroke, 32% reduced risk of depression and 40% of cognitive impairment (Psaltopoulou et al., 2013).

Comparable data on stroke incidence across European countries are lacking, as well as data which may relate different dietary patterns to stroke incidence in different countries. In the European Registers of Stroke (EROS) Study, population-based stroke registers were established in 6 European countries: France (Dijon); Italy (Sesto Fiorentino, northwest of Florence); Lithuania (Kaunas); the United Kingdom (London); Spain (Menorca); and Poland (Warsaw) (Heuschmann et al., 2009). Standardized criteria were used among these register including overlapping sources of notification. Overall, a source population of 1,087,048 inhabitants was observed, for a total of 2,129 patients with first stroke. Higher incidence rates of stroke were observed in eastern and lower rates in southern European countries, namely Italy and Spain. Total stroke incidence per 100,000, adjusted to the European population, ranged in men from 101.2 and 116.3 in Sesto Fiorentino and Menorca to 239.3 in Kaunas, and in women from 63.0 and 65.8 in Sesto Fiorentino and Menorca to 158.7 in Kaunas. Unfortunately, dietary habits were not available in the EROS Study, therefore we can only have indirect inference to suggest that lower rates observed in southern European countries (Spain and Italy) may in part depend on Mediterranean diet. We know from the EPIC survey that extra virgin olive oil is the most dominant source of MUFA in Italy and Spain, and Florence was one of the Italian centers involved in EPIC (Linseisen et al., 2009).

5. Conclusions

The effect of Mediterranean diet on vascular system, and on stroke in particular, relies undoubtedly on single components, but it is maximized in the diet considered as a whole. Moreover, the potential role of some components is still non completely understood. For instance, olive oil, with its content of oleic acid, is considered a major contributor to the beneficial effect of Mediterranean diet on the vascular system, in light of the protective associations with hypertension, diabetes, lipid profile, coronary artery disease, metabolic syndrome and obesity

(López-Miranda et al., 2010). However, olive oil contains hundreds of nonfat components with potential biological relevance, antioxidant and anti-inflammatory properties, including phenolic compounds, squalene, vitamin E, carotenoids, chlorophyll (Covas et al., 2006; Scarmeas and Dauchet, 2011). Also, more data are needed on the role of moderate wine consumption on incidence of and mortality from stroke and cardiovascular disease (Klatsky et al., 2003; Artero et al., 2015).

In 2013 the Mediterranean diet was inscribed on the Representative List of the Intangible Cultural Heritage of Humanity by UNESCO. In the motivations, it was underlined that “the Mediterranean diet involves a set of skills, knowledge, rituals, symbols and traditions concerning crops, harvesting, fishing, animal husbandry, conservation, processing, cooking, and particularly the sharing and consumption of food. Eating together is the foundation of the cultural identity and continuity of communities throughout the Mediterranean basin. It is a moment of social exchange and communication, an affirmation and renewal of family, group or community identity” (UNESCO, 2015).

Therefore, the cultural and social aspects of a Mediterranean way of eating are considered essential, together with the specific components of the diet. Unfortunately, as evidenced by Willet: “Ironically, the major benefactors in the research on the Mediterranean lifestyle and health have not been the Mediterranean countries”. For example, the countries of Northern Europe had the highest rates of cardiovascular disease in the world, but after adoption of many of the features of the Mediterranean diet, their life expectancy has increased dramatically. By contrast, lifestyles have changed in the Mediterranean area toward those of Northern Europe. The changes have not been in diet alone as the role of physical activity has also clearly declined (Willet, 2006).

In light of reported evidence, we can conclude that there is now a considerable amount of research suggesting the necessity for reappraisal, preservation and promotion of Mediterranean diet. Together with a healthy lifestyle, it is a cost-effective intervention to reduce the human, social and economic burden of stroke and cardiovascular disease.

Acknowledgements

The Authors thank Ms. Maria Elena Della Santa (Institute of Neuroscience, Italian National Research Council, Florence, Italy) for technical support in preparing the manuscript.

References

- Agnoli C, Krogh V, Grioni S, Sieri S, Palli D, Masala G, et al. 2011 A priori-defined dietary patterns are associated with reduced risk of stroke in a large Italian cohort. *J Nutr* 141, 1552-1558.
- Artero A, Artero A, Tarín JJ, Cano A. 2015 The impact of moderate wine consumption on health. *Maturitas* 80, 3-13.
- Boden-Albala B, Sacco RL. 2000 Lifestyle factors and stroke risk: exercise, alcohol, diet, obesity, smoking, drug use, and stress. *Curr Atheroscler Rep* 2, 160-166.
- Buckland G, Bach A, Serra-Majem L. 2008 Obesity and the Mediterranean diet: a systematic review of observational and intervention studies. *Obes Rev* 9, 582-593.
- Buckland G, González CA, Agudo A, Vilardell M, Berenguer A, Amiano P, et al. 2009 Adherence to the Mediterranean diet and risk of coronary heart disease in the Spanish EPIC Cohort Study. *Am J Epidemiol* 170, 1518-1529.
- Buckland G, Mayén AL, Agudo A, Travier N, Navarro C, Huerta JM, et al. 2012 Olive oil intake and mortality within the Spanish population (EPIC-Spain). *Am J Clin Nutr* 96,142-149.
- Covas MI, Nyyssönen K, Poulsen HE, Kaikkonen J, Zunft HJ, Kiesewetter H, et al., for the EUROLIVE Study Group. 2006 The effect of polyphenols in olive oil on heart disease risk factors: a randomized trial. *Ann Intern Med* 145, 333-341.
- Dearborn JL, Urrutia VC, Kernan WN. 2015 The case for diet: a safe and efficacious strategy for secondary stroke prevention. *Front Neurol* 6;doi:10.3389/fneur.2015.00001.
- Di Carlo A, Baldereschi M, Gandolfo C, et al. 2003 Stroke in an elderly population: incidence and impact on survival and daily function. The Italian Longitudinal Study on Aging. *Cerebrovasc Dis* 16,141-50.
- Di Carlo A. Human and economic burden of stroke. 2009 *Age Ageing* 38, 4-5.
- Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. PREDIMED Study Investigators. 2013 Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 368,1279-1290.
- Evers SM, Struijs JN, Ament AJ, van Genugten ML, Jager JH, van den Bos GAM. 2004 International comparison of stroke cost studies. *Stroke* 35,1209-1215.
- Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. 2009 Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. *Circulation* 119,1093-1100.

- Gardener H, Wright CB, Gu Y, Demmer RT, Boden-Albala B, Elkind MS, et al. 2011 Mediterranean-style diet and risk of ischemic stroke, myocardial infarction, and vascular death: the Northern Manhattan Study. *Am J Clin Nutr* 94, 1458-1464.
- He FJ, Nowson CA, MacGregor GA. 2006 Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet* 367, 320-326.
- Heuschmann PU, Di Carlo A, Bejot Y, Rastenyte D, Ryglewicz D, Sarti C, et al. for the European Registers of Stroke (EROS) Investigators. 2009 Incidence of stroke in Europe at the beginning of the 21st century. *Stroke* 40, 1557-1563.
- Hoevenaer-Blom MP, Nooyens AC, Kromhout D, Spijkerman AM, Beulens JW, van der Schouw YT, et al. 2012 Mediterranean style diet and 12-year incidence of cardiovascular diseases: the EPIC-NL cohort study. *PLoS One* 7:e45458. doi: 10.1371/journal.pone.0045458.
- Hu D, Huang J, Wang Y, Zhang D, Qu Y. 2014 Fruits and vegetables consumption and risk of stroke: a meta-analysis of prospective cohort studies. *Stroke* 45,1613-1619.
- Hulshof KF, Valsta LM, Welten DC, Löwik MR. 2001 Analytical approaches to food-based dietary guidelines in the European setting. *Public Health Nutr* 4, 667-672.
- Klatsky AL, Friedman GD, Armstrong MA, Kipp H. 2003 Wine, liquor, beer, and mortality. *Am J Epidemiol* 158, 585-595.
- Larsson SC, Virtamo J, Wolk A. 2013 Total and specific fruit and vegetable consumption and risk of stroke: a prospective study. *Atherosclerosis* 227, 147-152.
- Larsson SC, Wolk A. 2014 Dietary fiber intake is inversely associated with stroke incidence in healthy Swedish adults. *J Nutr* 144, 1952-1955.
- Linseisen J, Welch AA, Ocké M, Amiano P, Agnoli C, Ferrari P, et al. 2009 Dietary fat intake in the European Prospective Investigation into Cancer and Nutrition: results from the 24-h dietary recalls. *Eur J Clin Nutr* 63, S61-S80.
- Lock K, Pomerleau J, Causer L, Altmann DR, McKee M. 2005 The global burden of disease attributable to low consumption of fruit and vegetables: implications for the global strategy on diet. *Bull World Health Organ* 83, 100-108.
- López-Miranda J, Pérez-Jiménez F, Ros E, De Caterina R, Badimón L, Covas MI, et al. 2010 Olive oil and health: summary of the II international conference on olive oil and health consensus report, Jaén and Córdoba (Spain) 2008. *Nutr Metab Cardiovasc Dis* 20, 284-294.
- Martínez-González MA, de la Fuente-Arrillaga C, Nunez-Cordoba JM, Basterra-Gortari FJ, Beunza JJ, Vazquez Z, et al. 2008 Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. *BMJ* 336, 1348-1351.
- Misirli G, Benetou V, Ligiou P, Bamia C, Trichopoulos D, Trichopoulou A. 2012 Relation of the traditional Mediterranean diet to cerebrovascular disease in a Mediterranean population. *Am J Epidemiol* 176,1185-1192.
- Mizrahi A, Knekt P, Montonen J, Laaksonen MA, Heliövaara M, Järvinen R. 2009 Plant foods and the risk of cerebrovascular diseases: a potential protection of fruit consumption. *Br J Nutr* 102, 1075-1083.
- Nagura J, Iso H, Watanabe Y, Maruyama K, Date C, Toyoshima H, et al. for the JACC Study Group. 2009 Fruit, vegetable and bean intake and mortality from cardiovascular disease among Japanese men and women: the JACC Study. *Br J Nutr* 102, 285-292.
- Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, Rayner M. European Cardiovascular Disease Statistics 2012. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis, 2012.
- Nordmann AJ, Suter-Zimmermann K, Bucher HC, Shai I, Tuttle KR, Estruch R, et al. 2011 Meta-analysis comparing Mediterranean to low-fat diets for modification of cardiovascular risk factors. *Am J Med* 124, 841-851.
- O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al., for INTERSTROKE investigators. 2010 Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 376, 112-123.
- Psaltopoulou T, Naska A, Orfanos P, Willopoulos D, Mountokalakis T, Trichopoulou A. 2004 Olive oil, the Mediterranean diet, and arterial blood pressure: the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Am J Clin Nutr* 80, 1012-1018.
- Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kostis R, Scarmeas N. 2013 Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. *Ann Neurol* 74, 580-591.
- Salas-Salvadó J, Fernández-Ballart J, Ros E, Martínez-González MA, Fitó M, Estruch R, et al. for the PREDIMED Study Investigators. 2008 Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. *Arch Intern Med* 168, 2449-2458.
- Samieri C, Féart C, Proust-Lima C, Peuchant E, Tzourio C, Stapf C, et al. 2011 Olive oil consumption, plasma oleic acid, and stroke incidence: the Three-City Study. *Neurology* 77, 418-425.
- Scarmeas N, Dauchet L. 2011 Olive oil: pertinent to neurologic diseases too? *Neurology* 77, 412-413.
- Schwingshackl L, Hoffmann G. 2014 Monounsaturated fatty acids, olive oil and health status: a systematic review and meta-analysis of cohort studies. *Lipids Health Dis* 13, 154.
- Sharma S, Cruickshank JK, Green DM, Vik S, Tome A, Kolonel LN. 2013 Impact of diet on mortality from stroke: results from the U.S. multiethnic cohort study. *J Am Coll Nutr* 32, 151-159.
- Sofi F, Abbate R, Gensini GF, Casini A. 2010 Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr* 92,1189-1196.
- Strong K, Mathers C, Bonita R. 2007 Preventing stroke: saving lives around the world. *Lancet Neurol* 6, 182-187.
- Tikk K, Sookthai D, Monni S, Gross ML, Lichy C, Kloss M, et al. 2014 Primary preventive potential for stroke by avoidance of major lifestyle risk factors: the European Prospective Investigation into Cancer and Nutrition-Heidelberg cohort. *Stroke* 45,2041-2046.
- UNESCO. Culture. Intangible heritage list. Mediterranean diet. Available at: <http://www.unesco.org/culture/ich/RL/00884>. Accessed March 2015.
- Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, et al. 1995 Mediterranean diet pyramid: a cultural model for healthy eating. *Am J Clin Nutr* 61, 1402S-1406S.
- Willett WC. 2006 The Mediterranean diet: science and practice. *Public Health Nutr* 9, 105-110.