Quale ruolo della medicina complementare nella neurologia di oggi
Milano, 5 febbraio 2014

Ictus
La malattia e i fattori di rischio

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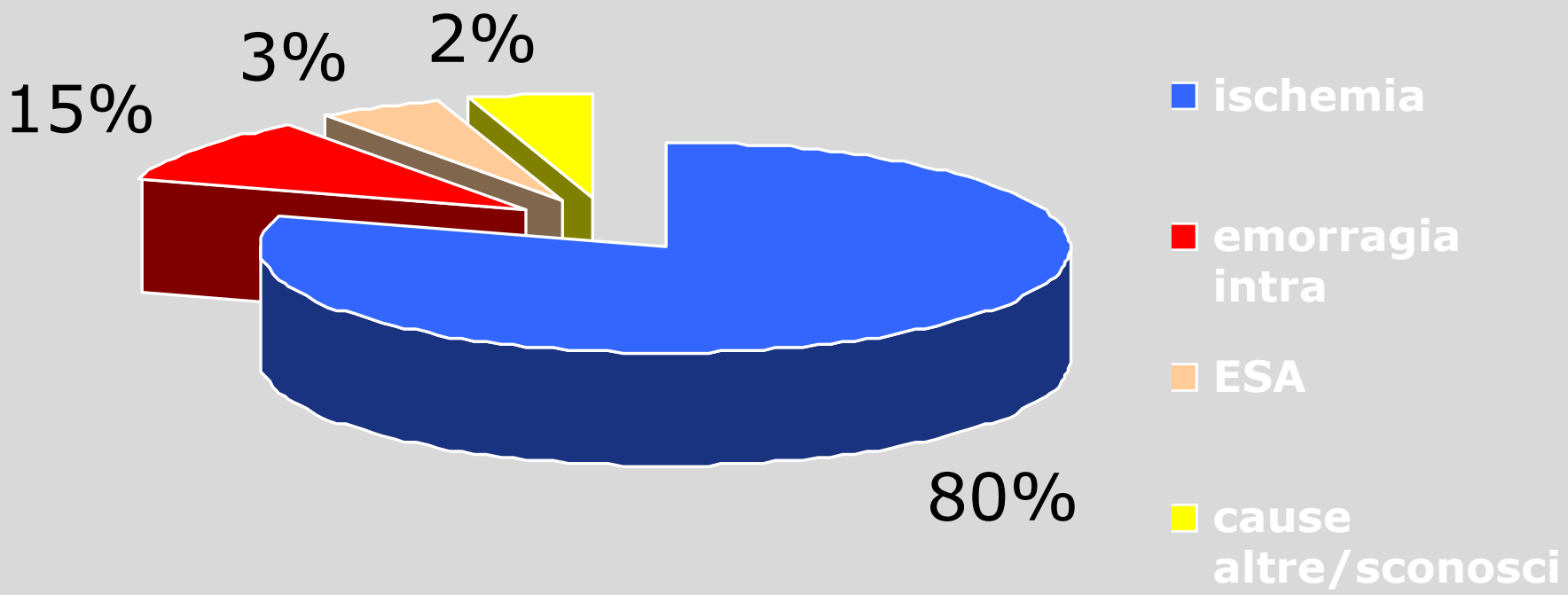
Outline

- Definition of stroke
- Classifications of ischemic stroke
- Pathogenetic mechanisms of ischemic damage
- Risk factors
  - ….
  - Diet

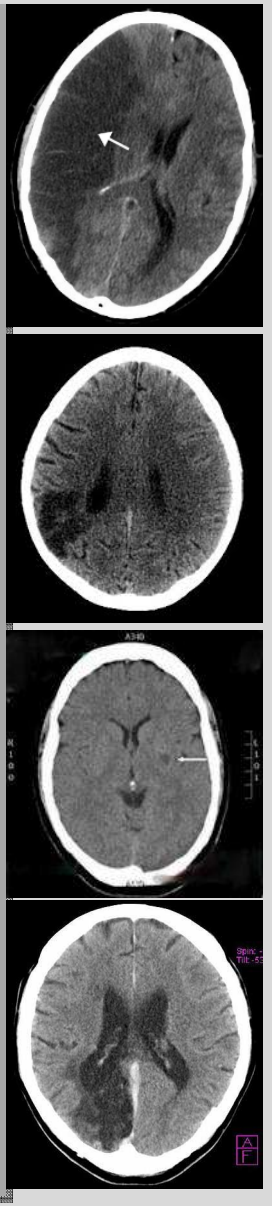
OMS definition of stroke

ICTUS: sindrome clinica caratterizzata dallo sviluppo rapido di sintomi e/o segni clinici di deficit neurologico focale (a volte globale), la cui sintomatologia perdura per più di 24 ore.



Oxfordshire Community Stroke Project (OCSP) classification

- total anterior circulation strokes (TACS): triad of hemiparesis (or hemisensory loss), dysphasia (or other new higher cortical dysfunction), and homonymous hemianopia;
- partial anterior circulation stroke (PACS): two of the features of TACS, or isolated dysphasia or parietal lobe signs;
- lacunar strokes (LACS): pure motor stroke, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, or dysarthria-clumsy hand syndrome;
- posterior circulation stroke (POCS): patients with brain stem or cerebellar signs, and/or isolated homonymous hemianopia



Bamford J et al. J Neurol Neurosurg Psychiatry 1990; 53:824–9.

Etiologic Classification of Ischemic Stroke

Subtype Category	Classification System		
	TOAST	CCS	ASCO1
Cardioembolism/cardioaortic	123/354 (34.7%)	132/354 (37.3%)	119/354 (33.6%)
Large artery/atherothrombosis	32/354 (9.0%)	47/354 (13.3%)	38/354 (10.7%)
Small artery occlusion/ disease	47/354 (13.3%)	62/354 (17.5%)	37/354 (10.5%)
Other determined causes	12/354 (3.4%)	22/354 (6.2%)	16/354 (4.5%)
Cause undetermined/no ASCO1 evidence for a single etiology	140/354 (39.6%)	91/354 (25.7%)	144/354 (40.7%)

Table 1. Distribution of Cerebral Infarctions According to Age in the Sagrat Cor Hospital of Barcelona Stroke Registry

Subtype of Cerebral Infarction (n = 1840)	Years of Age			
	< 65 (n= 314)	65–74 (n=501)	75–84 (n=722)	≥ 85 (n=303)
Cardioembolic	46 (14.6)	100 (20)	213 (29.5)	109 (36)
Atherothrombotic	66 (21.0)	159 (31.7)	233 (32.3)	95 (31.4)
Lacunar	93 (29.6)	159 (31.7)	173 (24)	59 (19.5)
Unknown cause	61 (19.4)	69 (13.8)	81 (11.2)	37 (12.2)
Unusual cause	48 (15.3)	14 (2.8)	22 (3.0)	3 (1)

Clinical severity – National Institutes of Health Stroke Scale

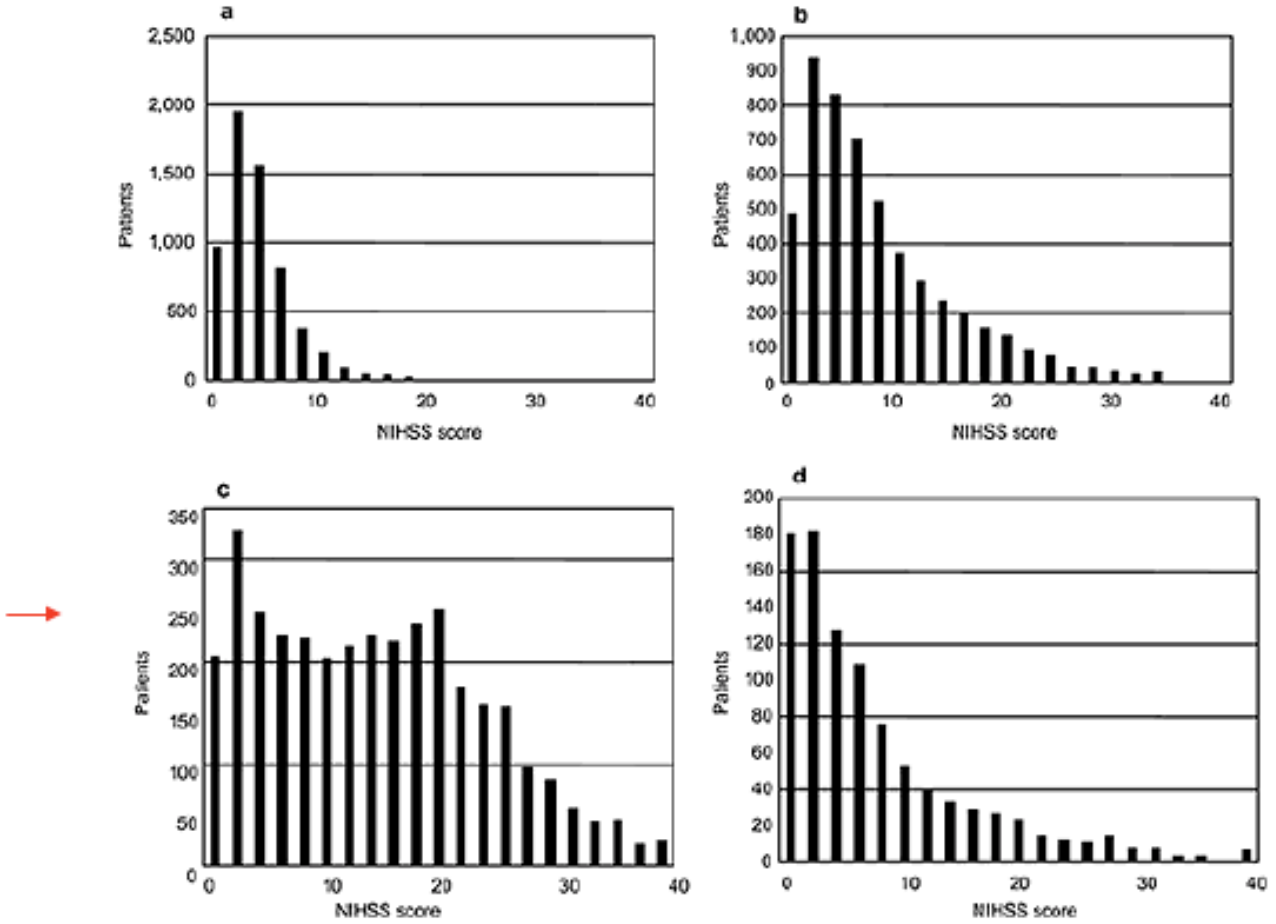
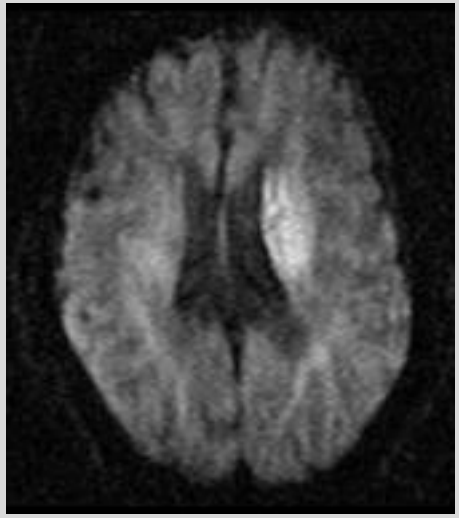
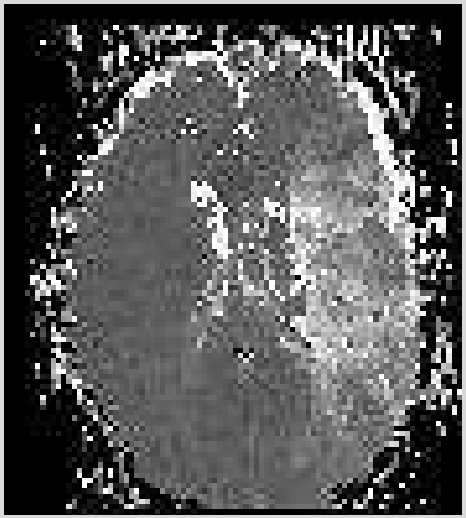
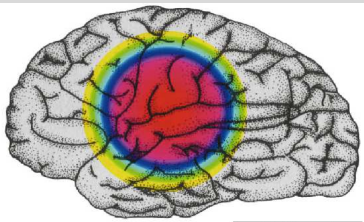


Fig. 1. Distribution of NIHSS scores for each stroke subtype.
a Lacunar stroke. **b** Atherothrombotic stroke. **c** Cardioembolic stroke. **d** Other.

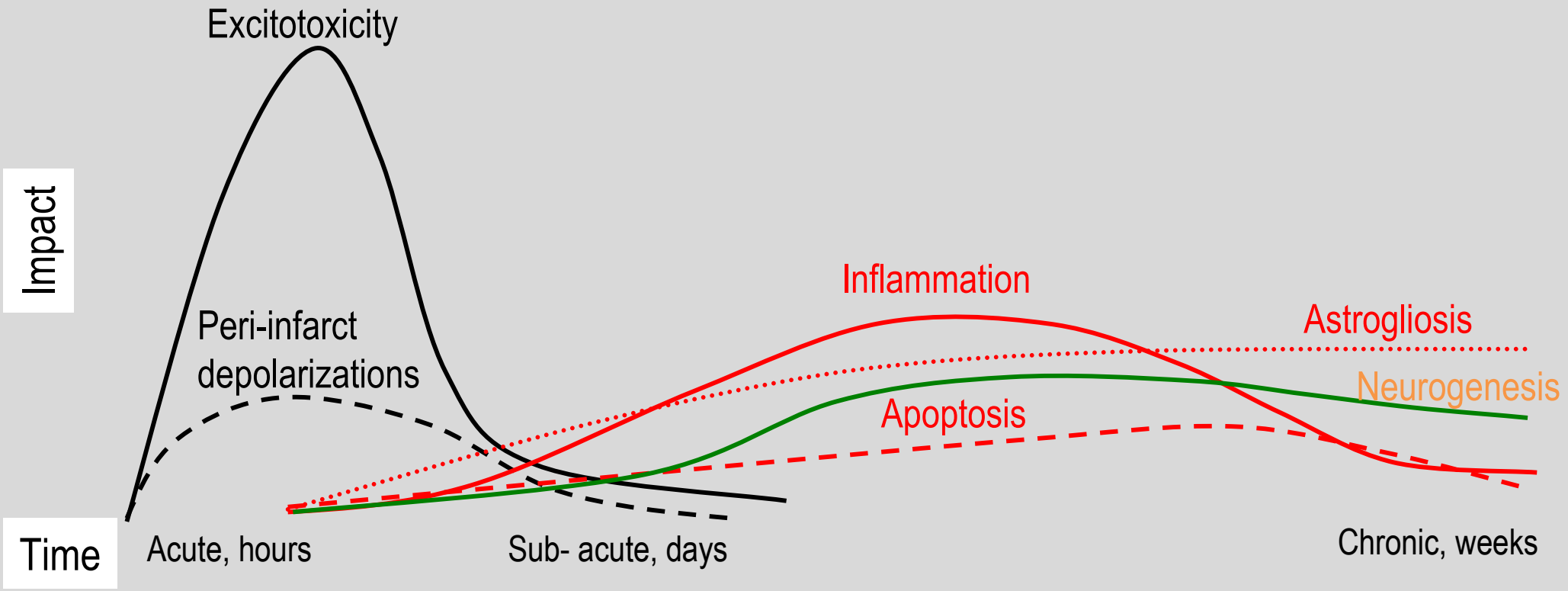
Kimura et al Cerebrovasc Dis 2004







Morphology		Biochemistry
Infarction	CORE	Ionic failure Anoxic depolarization Glucose use ↓
	PENUMBRA	Glutamate release Glucose use ↑ Protein synthesis ↓ Acidosis Oxygen extraction ↑
Inflammation and apoptosis		Selective gene expression



ACUTE PHASE (immediately)

Direct tissue damage caused by lack of metabolic substrates, depolariztion of cellular membranes

SUBACUTE PHASE (> 6h)

Ischemic core enlarges to peri-ischemic penumbral area (ca 4-6h) until they merge. Oedema

CHRONIC PHASE (days-weeks)

Secondary phenomena: oedema, inflammation, delayed cell death, tissue plasticity

Risk factors for ischemic stroke

- **Non modificabili**
  - Età
  - Sesso
  - Fattori genetici
  - Razza/Etnia

- **Modificabili**

  Ben documentati
  - Ipertensione arteriosa
  - Coronaropatia e PAD
  - Fibrillazione atriale
  - Diabete mellito
  - TIA
  - Stenosi carotidea asintomatica
  - Dislipidemia (col tot elevato o col HDL ridotto)
  - Iperomocisteinemia
  - Fumo di sigaretta
  - Eccessivo consumo di alcool
  - **Dieta**
  - Sedentarietà

  Meno documentati
  - Sindrome metabolica
  - Obesità (IMC>30 kg/m^2)
  - Abuso di droga
  - Ipercoagulabilità
  - Terapia ormonale sostitutiva / contraccettivi orali
  - Processi infiammatori / infezioni acute
  - Emicrania
  - OSAS
  - Inquinamento atmosferico

Tipo di ictus ischemico	Fattori di rischio prevalentemente coinvolti
Aterotrombotico	Ipertensione
	Fumo di sigaretta
	Ipercolesterolemia
	Abuso di alcol (raccomandato 12 gr nelle donne, 24 gr negli uomini) (grado alcolico x 0.8 x ml / 100)
	Iperomocisteinemia
Cardioembolico	Età
	Cardiopatia ischemica
	Fibrillazione atriale
	Scompenso cardiaco
Lacunare	Ipertensione arteriosa
	Diabete

Alimenti e nutrienti

- CEREALI
- PATATE
- CARNI
- PRODOTTI PESCA
- UOVA
- LEGUMI SECCHI
- LATTE
- DERIVATI
- FRUTTA/ORTAGGI /LEGUMI FRESCHI
- GRASSI da CONDIMENTO

Table 2. Effects of foods and nutrients on the risk of stroke[a]

Items	*Relationship*	*Effects*
Foods		
Rice	Intake is not associated with risk of stroke.	Not clear
Whole grains	High intake is associated with a 21% (95% CI 15–27) lower incidence of cardiovascular events.	Positive
Legumes	Randomized trials have shown that isolated soy protein or isoflavones (phytoestrogens) lower diastolic blood pressure by 2 mm Hg and LDL cholesterol by 3%.	Positive
Total meat	Each daily serving is associated with a 24% (95% CI 8–43) increased risk of stroke.	Negative
Processed meat	Consumption was associated with an increased risk of stroke in one observational study but not in another	Negative
Fish	Increased consumption by three servings per day is associated with a 6% (95% CI 1–11) lower risk of stroke.	Positive
Milk	Consumption is not associated with risk of stroke.	Not clear
Reduced-fat milk (vs full-strength milk)	Consumption is associated with lower risk of stroke.	Positive
Fruit and vegetables	Consumption of more than five servings of fruit and vegetables per day is associated with a 26% (95% CI 21–31) lower risk of stroke. Consumption of more than five servings per day lowers blood pressure by 4.0/1.5 mm Hg.	Positive
Coffee	Moderate consumption (3–4 cups per day) is associated with a 17% (95% CI 8–26) lower risk of stroke.	Positive
Tea	Moderate consumption (⩾3 cups per day) is associated with a 21% (95% CI 15–27) lower risk of stroke.	Positive
Sugar-sweetened beverages	High intake is associated with increased obesity, diabetes, metabolic syndrome and coronary heart disease.	Negative
Nutrients		

[Lim and Choue, European Journal of Clinical Nutrition 2013]

Whole grain

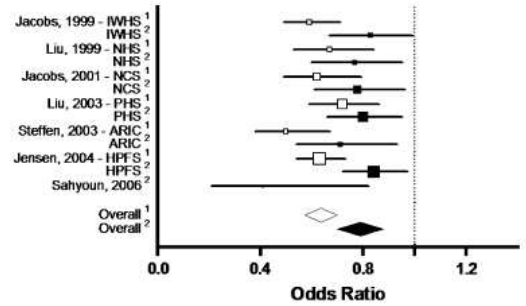


Figure 1 Odds ratios of incident cardiovascular disease, comparing high versus low whole grain intake. Abbreviations: IWHS — Iowa Women's Health Study; NHS — Nurses' Health Study; NCS — Norwegian County Study; PHS — Physicians' Health Study; ARIC — Atherosclerosis Risk in Communities; HPFS — Health Professionals' Follow-up Study. [1]Demographic-adjusted model. [2]Demographic + risk factor adjusted model.

2.5 vs 0.2 servings/day → 37% lower risk of incident cardiovascular disease

Table 3 Examples of whole grain foods and flours

Amaranth
Barley
Buckwheat
Corn *(whole cornmeal, popcorn)*
Millet
Oats *(oatmeal)*
Qinoa
Rice *(brown rice)*
Rye
Sorghum *(or milo)*
Teff
Triticale
Wheat *(varieties include spelt, emmer, farro, einkorn, Kamut®, durum; forms include bulgur, cracked wheat, and wheatberries)*
Wild rice

When consumed in a form retaining the bran, germ, and endosperm components. Source: The Whole Grains Council (http://www.wholegrainscouncil.org).

Amaranth (India)
orzo
grano saraceno
mais
miglio
avena
Quinoa (Ande)
riso intergrale
segale
saggina
Teff (Etiopia)
grano
riso selvatico

- Beneficial effects on glucose homeostasis
  - Reduced insulin resistance
  - Lower risk of incident T2DM

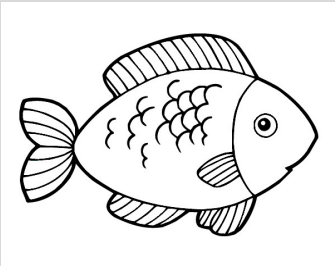
- Effects on lipid (Beta-glucan, phytosterol)

- Inverse relationship between intake of soluble fiber and LDL cholesterol (increased bile acid degradation; phytosterol competes with cholesterol for absorption in the small intestine)

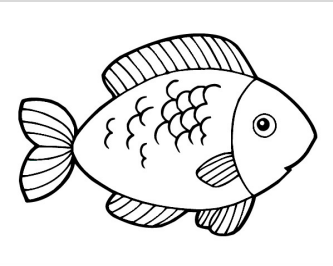
- Endothelial function (antioxidants, including vitamin E; phytoestrogens)

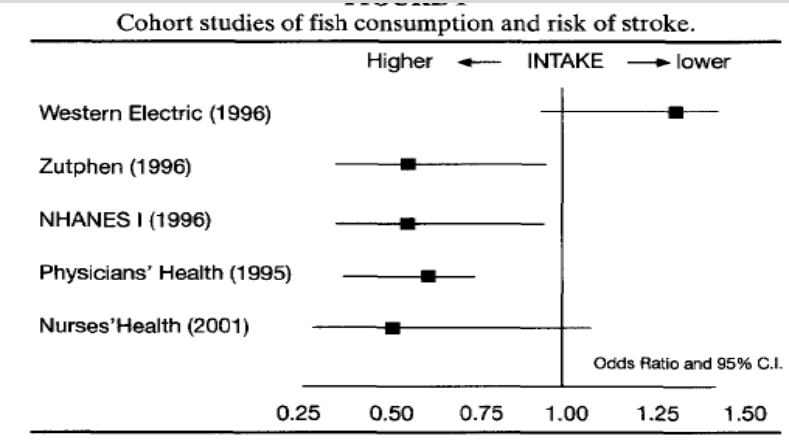
- improve vascular reactivity, a marker of endothelial function, in response to a high fat meal

Mellen PB et al. Nutrition, Metabolism & Cardiovascular Diseases (2008) 18, 283-290



Fish



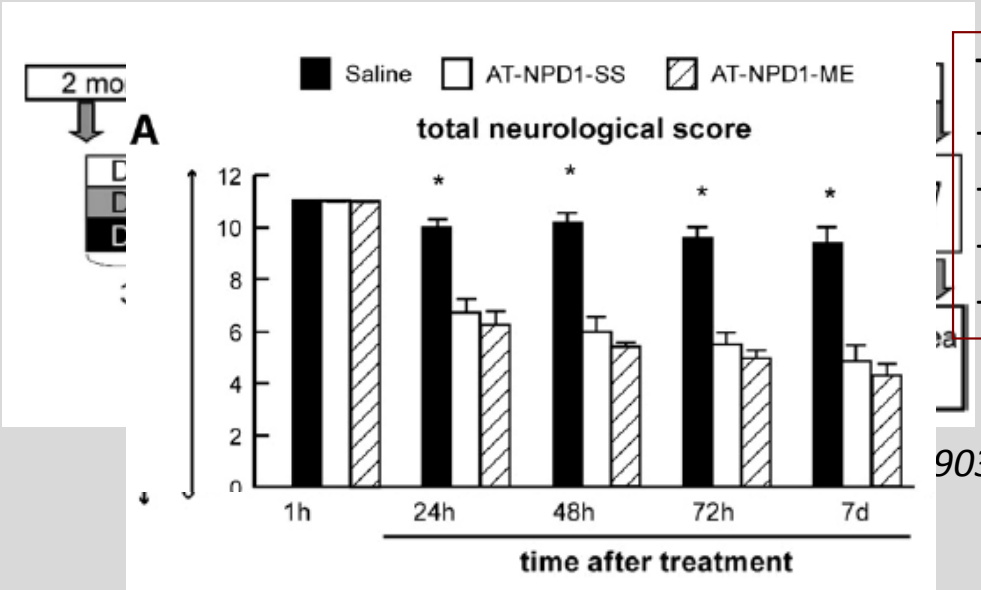


n-3 polyunsaturated fatty acids

eicosapentaenoic acid (EPA)

docosahexaenoic acid (DHA) is the precursor of novel mediators including resolvins and protectins:

- neuroprotectin D1 (NPD1), a potent regulator of PMN infiltration at the level of retina and brain,
- Aspirin-triggered Neuroprotectin D1 (AT-NPD1)



DHA-enriched diet:
- Attenuates microglial activation
- Decreases ischemic lesion
- Increases levels of anti-inflammatory n-3 PUFA
- Decreases levels of pro-inflammatory n-6 PUFA

Shifting upward n-3/n-6 PUFA ratio reduce COX induction, inducing the production of less inflammatory derivatives (IL-β)

Treatment with AT-NDP1 (-SS and –ME):
- Improved neurological scores
- Reduced total lesion volumes at brain MR
- Decreased water content in the striatum at day 7
- Reduced infarct volume at histopathology analysis

Bazan NG et al. Experimental Neurology 2012;238:122

903

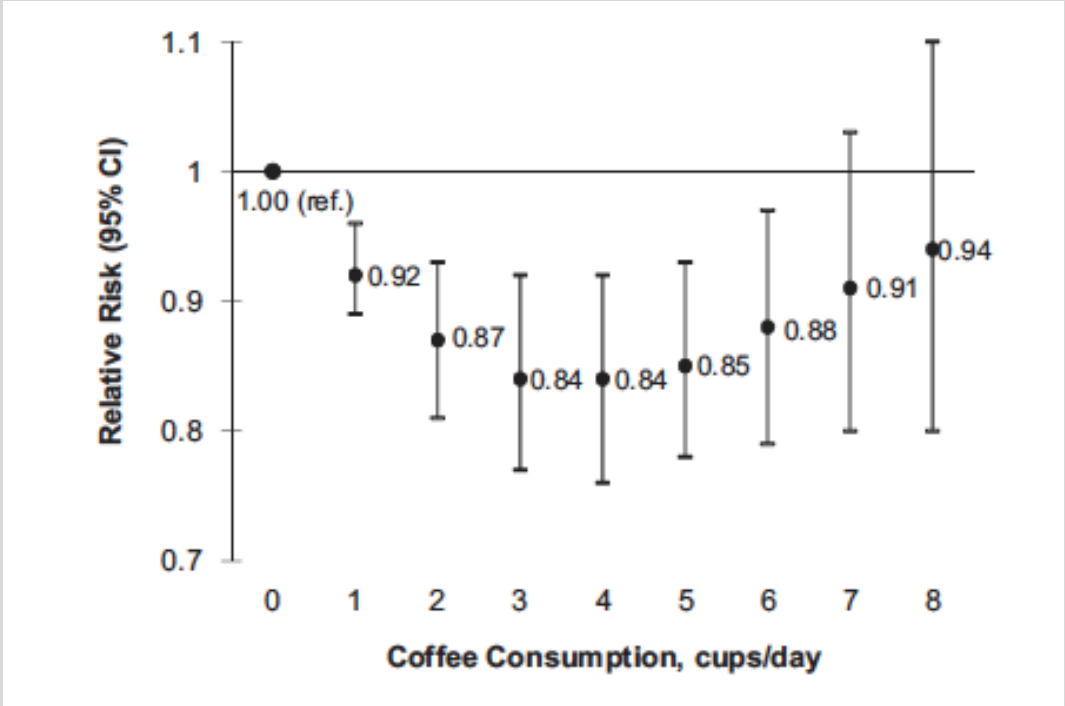


Six very large studies have consistently shown a 27 to 55% lower incidence of stroke and reduced mortality from stroke in the groups with highest consumption of fruit and vegetable foods, The studies on the effects of different vegetables indicated that all categories of fruits and vegetables may play a protective role, with a more marked effect for cruciferous vegetables, green leafy vegetables and citrus fruits. Potatoes are not included among the protective vegetables nor are mushrooms, onions, garlic and stalk vegetables. A protective effect of fruit and vegetables has been demonstrated for a consumption of at least 500 g/day

Joshipura, JAMA 1999

Coffee

- The most abundant bioactive compounds in coffee are caffeine, diterpenes (present in the oil), and polyphenols.
  - Caffeine is a stimulant that induces a transient increase in blood pressure. However, a meta-analysis of 10 RCTs of the long-term effect of coffee consumption in mainly healthy, normotensive individuals found no significant changes in systolic blood pressure or diastolic blood pressure
  - The diterpenes cafestol and kahweol have cholesterol-raising properties. The diterpenes are extracted from the coffee beans by hot water but are retained by a paper filter.
  - Polyphenols, most notably chlorogenic acid (CGA), possess antioxidant activities in vitro. However, there is controversy on whether chlorogenic acid and other polyphenols in coffee could suppress the oxidative modification of LDL particles in humans. As opposed to caffeine, CGA have been demonstrated to have antihypertensive effects, possibly via nitric oxide–mediated vasodilation.



Results from a meta-analysis of 11 prospective studies involving 479 689 participants and 10 003 stroke cases showed a nonlinear relationship between coffee consumption and stroke risk.

Three prospective studies on coffee consumption and stroke were published since the meta-analysis. Two of them confirmed an inverse association of moderate coffee consumption with stroke incidence or mortality. Findings from a large prospective cohort of 229 119 US men and 173 141 US women showed an inverse association between

moderate coffee consumption and stroke mortality

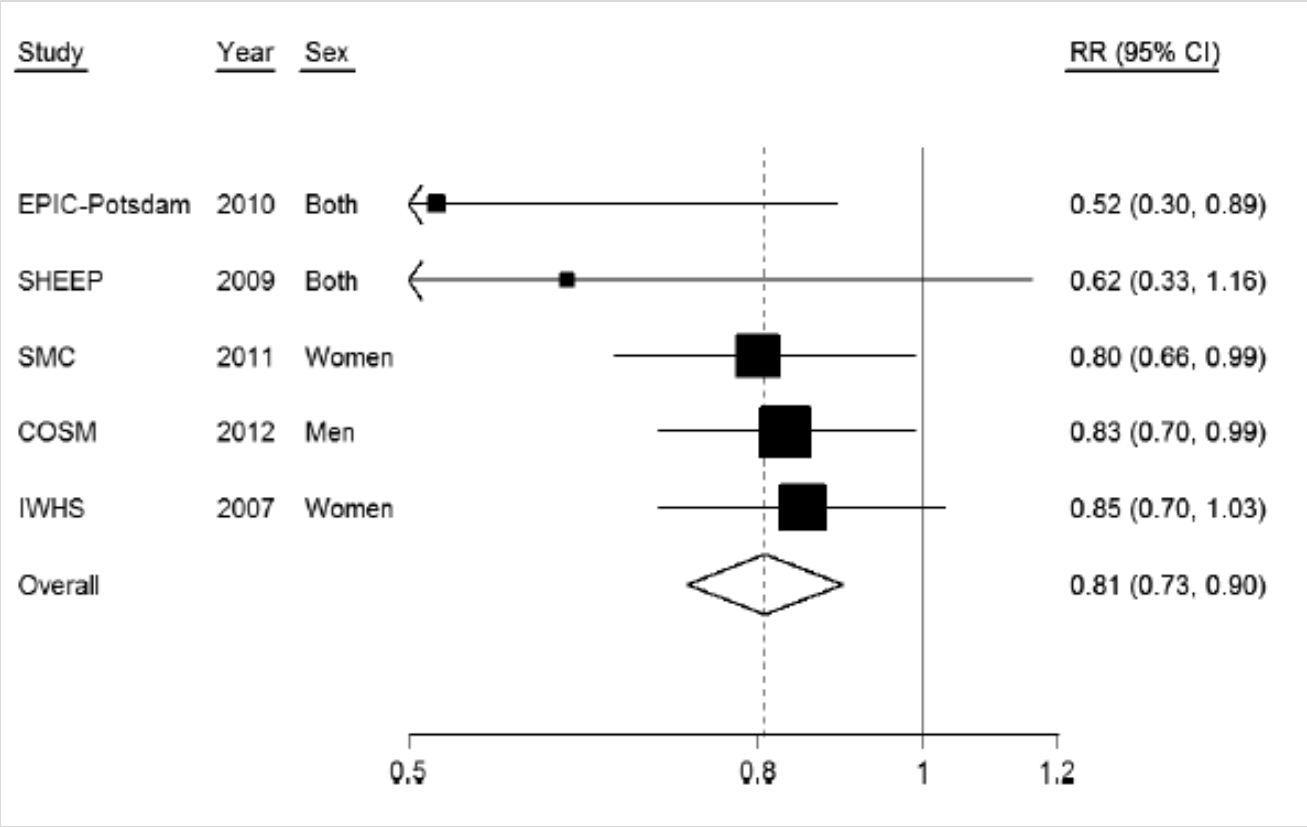
Larsson SC, Orsini N. Am J Epidemiol 2011;174:993–1001.

Black and green tea

- Tea is produced from the leaves of the plant *Camellia sinensis and* can be classified by degree of fermentation: black tea (fermented), predominantly consumed in Western countries; oolong tea (partially fermented), primarily consumed in Southern China and Taiwan; and green tea (unfermented), mainly consumed in Asia. All types of tea are rich in various flavonoids. Tea and tea-derived flavonoids have been demonstrated:
  - to have protective effects on oxidation of low-density lipoproteins
  - to improve endothelium-dependent flow-mediated dilatation
  - to have antithrombotic and anti-inflammatory effects

- In a meta-analysis of 14 prospective studies of green or black tea consumption, the overall RR of total stroke for a 3-cup/d increment in tea consumption was 0.87 (95% CI, 0.81–0.94). *Shen L et al. J Zhejiang Univ Sci B. 2012;13:652–662.*
- Results from a cohort of 82 369 Japanese men and women showed a significant 20% reduced risk of total stroke among those who consumed >4 cups/d of green tea. *Kokubo Y et al. Stroke. 2013;44:1369–1374.*
- In a cohort of 74 961 Swedish men and women, consumption of >4 cups/d of black tea, compared with no consumption, was associated with a significant 21% lower risk of total stroke. *Larsson SC et al. Ann Epidemiol. 2013;23:157–160.*

Chocolate



The few prospective studies of chocolate consumption in relation to stroke risk have reported either a statistically significant or a non-significant inverse association.

Results from a meta-analysis of those 5 studies (4 from Europe and 1 from the United States) showed a significant 19% lower risk of stroke when comparing the highest with the lowest category of chocolate consumption.

Larsson SC. Stroke. 2014;45:309-314.

- Antioxidant vitamins
  - Vitamin A and beta-carotene
    - A meta-analysis of 3 randomized controlled trials (RCTs) of beta-carotene in a total of 82 483 participants showed no effect of beta-carotene on the rate of stroke compared with control (OR, 1.0; 95% CI, 0.91–1.09; *P0.92).* Moreover, beta-carotene was associated with an increased risk of cardiovascular mortality (OR, 1.10; 95% CI, 1.03– 1.17; *P0.003) and all-cause mortality (OR, 1.07; 95% CI* 1.02–1.11; *P0.003).*
  - Vitamin C
    - Large observational epidemiological studies suggest that increasing plasma vitamin C concentrations are associated with a reduced risk of stroke. However, observational studies cannot eliminate bias and confounding. Three large RCTs (Heart Protection Study, Women's Antioxidant Cardiovascular Study, Physicians' Health Study II) which minimize bias and confounding, have shown no effect of vitamin C on stroke risk.
  - Vitamin E
    - A recent meta-analysis of 13 RCTs of vitamin E in 166 282 participants showed no significant benefit of vitamin E in the prevention of stroke of any type (RR, 1.01; 95% CI, 0.96–1.07), ischemic stroke (RR, 1.01. 95% CI, 0.94–1.09), or hemorrhagic stroke (RR, 1.12; 95% CI, 0.94–1.33).
- B Vitamins
  - Folic Acid and Vitamin B12
    - A meta-analysis of RCTs of folic acid supplementation in 37 485 patients showed a lack of effect of folic acid on all stroke (RR, 0.96; 95% CI, 0.87–1.06) A subsequent meta-analysis of 237 genetic epidemiological studies, in which the dietary folate status, tHcy, and the presence of the methylene tetrahydrofolate reductase C677T polymorphism of 60 000 individuals were correlated with 20 885 stroke events, predicted a lack of effect of lowering tHcy in preventing stroke in regions with established or increasing folate intake. It remains uncertain, however, whether supplementation with folic acid and vitamin B12 may prevent stroke in populations with low intake of folate or vitamin B12.
  - Vitamin B3 (Niacin)
    - A systematic review and meta-analysis of 11 RCTs of niacin alone, or in combination with other lipid-lowering drugs, published between January 1966 and August 2008 reported that among 2682 patients who were randomly allocated to niacin (1–3 g/day), there was a significantly reduced rate of stroke (OR, 0.74; 95% CI, 0.59–0.92). HPS2-THRIVE (Heart Protection Study-Treatment of High density lipoprotein to Reduce the Incidence of Vascular Events) ongoing.

Hankey, GJ. Stroke. 2012;43:2814-2818

Limitations of observational epidemiological studies: the Vitamin D model

Vitamin D levels and risk of stroke

A recent meta-analysis of 7 prospective studies that examined 25-hydroxyvitamin D levels in relation to the occurrence of stroke in 1214 individuals reported that low 25-hydroxyvitamin D levels were associated with an increased risk of stroke in comparison to high levels (pooled RR, 1.52; 95% CI, 1.20 –1.85). [Sun, Stroke 2012]

Effect of Vitamin D Supplementation on Stroke

There is no reliable evidence from randomized controlled trials to support or refute a causal association between vitamin D status and stroke.

The VITamin D and OmegA-3 triaL (VITAL) is currently randomizing 20 000 people to receive 2000 IU of vitamin D3 (cholecalciferol) per day or placebo as well as 1 g of marine omega-3 fatty acids per day or placebo for 5 years. The primary outcome of the study is total cancer and major cardiovascular events (a composite of myocardial infarction, stroke, and death due to cardiovascular events). [Manson, Cleve Clin J Med. 2010]

Table 2. Limitations of Observational Epidemiological Studies in Unraveling the Relationship Between Vitamin D and Stroke

Confounding
Several factors are associated with both a low vitamin D and a high risk of stroke.
For example, low socioeconomic status, cigarette smoking, physical inactivity, obesity.
If these factors are not recorded, not measured, or measured inaccurately, statistical models will fail to appropriately adjust for their effect on the interaction between vitamin D and risk of stroke.
Bias: Reverse causality
The effects of a stroke may subsequently lead to a lower vitamin D concentration in the blood.
For example, acute stroke may result in acute inflammation, which can reduce vitamin D.
For example, stroke may cause a disability such as hemiparesis that restricts outdoor activity and therefore exposure to sunlight, which is a key determinant of vitamin D concentration.
Bias: Publication and citation
Studies with null or negative results are less likely to be published and cited than studies with positive results, particularly if there is an anticipation or perception of a positive association.

[Graeme, Stroke 2012]

Thank-you for your attention