Nutrition and the risk of stroke

Graeme J Hankey

Lancet Neurol 2012; 11: 66–81

This online publication has been corrected. The corrected version first appeared at thelancet.com/neurology on December 22, 2011

Department of Neurology, Royal Perth Hospital, Western Australia (Prof G J Hankey FRACP)

Correspondence to: Prof Graeme J Hankey, Department of Neurology, Royal Perth Hospital, 197 Wellington Street, Perth, Western Australia, 6001 Australia
gjhankey@cyllene.uwa.edu.au

Poor nutrition in the first year of a mother's life and undernutrition in utero, infancy, childhood, and adulthood predispose individuals to stroke in later life, but the mechanism of increased stroke risk is unclear. Overnutrition also increases the risk of stroke, probably by accelerating the development of obesity, hypertension, hyperlipidaemia, and diabetes. Reliable evidence suggests that dietary supplementation with antioxidant vitamins, B vitamins, and calcium does not reduce the risk of stroke. Less reliable evidence suggests that stroke can be prevented by diets that are prudent, aligned to the Mediterranean or DASH (Dietary Approaches to Stop Hypertension) diets, low in salt and added sugars, high in potassium, and meet, but do not exceed, energy requirements. Trials in progress are examining the effects of vitamin D and marine omega-3 fatty acid supplementation on incidence of stroke. Future challenges include the need to improve the quality of evidence linking many nutrients, foods, and dietary patterns to the risk of stroke.

Introduction

Between 1970 and 2008, the incidence of stroke in high-income countries fell by 42%, from 163 (95% CI 98–227) to 94 (72–116) per 100 000 person years.[1] This decline coincided with increased public awareness of the dangers to health posed by high blood pressure, high blood cholesterol, and cigarette smoking, and reduced prevalence of these risk factors in the population.[2] By contrast, between 1970 and 2008, the incidence of stroke in low-income and middle-income countries increased by more than 100%, from 52 (95% CI 33–71) to 117 (79–156) per 100 000 person years.[1] This increase coincided with food and lifestyle changes arising from industrialisation and urbanisation.[3,4] Modernisation, overconsumption of calories, and increased prevalence of obesity, metabolic syndrome, and type 2 diabetes mellitus threaten to stem the decline of stroke incidence in high-income countries and to accelerate the increase in stroke incidence in low-income and middle-income countries.[5–7] Accurately assessing and understanding the role of nutrition in the causes and consequences of stroke will be crucial in developing and implementing strategies to minimise the global burden of stroke.[8–12] The aim of this Review is to examine the evidence linking nutrition and diet to the risk of stroke.

Nutritional status

What is malnutrition?

Malnutrition has no universally accepted definition but describes a deficiency, excess, or imbalance in a wide range of nutrients, resulting in a measurable adverse effect on body composition, function, and clinical outcome.[13] Undernutrition describes a long-standing deficiency of essential nutrients, most commonly energy (kJ or calories) and protein,[14] whereas overnutrition describes an excess intake of nutrients (most commonly saturated fats and carbohydrates) for metabolic and health requirements.

How is nutritional status assessed?

Nutritional assessment is not standardised. The simplest measure of nutritional status is bodyweight, but it can be confounded by height and ethnic origin, and, in severe protein malnutrition, by fluid retention due to hypoalbuminaemia.

Body fat content is estimated by body mass index (BMI), which is a measure of weight in kilograms divided by the square of height in metres.[15] Adults with a BMI of 18·5–24·9 kg/m² are categorised as being of normal weight, individuals with a BMI of 25·0 to 29·9 kg/m² as overweight, and those with a BMI of 30 kg/m² or more as obese.[15] A drawback of this measure is that different ethnic groups have different proportions of fat to lean tissue at equivalent BMIs.[16]

Other measures of nutritional status include indicators of visceral adiposity, such as the waist-to-hip ratio, waist-to-height ratio, and waist circumference,[17] and indicators of protein status, such as serum albumin and prealbumin concentrations.[18–20]

How common is malnutrition?

Undernutrition is common, under-recognised, and undertreated. In the UK, about 5% of the population have a BMI of below 18·5 kg/m².[13] In UK hospitals, the prevalence of malnutrition is reported to range from 13% to 40%.[18,21] The prevalence of undernutrition increases at least two times in the elderly and in those with chronic disease, and three times in people living in institutional care, such as survivors of stroke.[13,14] The elderly are especially prone to deficiencies of specific micronutrients such as folate.[13] Malnutrition is also common in situations of poverty, social isolation, and substance misuse.

An estimated 1·46 billion adults and 170 million children worldwide are now classified as overweight, including 502 million adults who are obese.[5] In the USA, two-thirds of adults are overweight and one-third obese,[6,22] and the incidence and prevalence of being overweight or obese in children and adults are increasing.[5–7,22–24]

Is malnutrition a risk factor for stroke?

The methods used to investigate the effects of nutritional factors on the risk of stroke have limitations (panel 1),[27] and the results of such studies should be interpreted with caution, bearing in mind the criteria that need to be fulfilled to establish a causal association between a risk factor and disease.[28,29]

Undernutrition

Mother and fetus

Observational studies suggest that poor nutrition in the first year of a woman's life leads to deformity of the bony pelvis.[30,31] During subsequent pregnancy in adulthood, a flat pelvis impairs the mother's ability to sustain growth of the placenta and fetus, as manifest by lower placental weight, smaller head circumference, and lower birthweight of the baby.[30,31] In turn, these factors seem to be associated with an increased risk of stroke in the mother's offspring.[30,31] The mechanism by which poor maternal nutrition and poor growth in utero might increase the risk of stroke could be linked to hypertension and raised plasma fibrinogen concentrations in adulthood, and a permanent adverse effect on vascular structure and function.[32,33]

Children

Observational evidence suggests that poor growth in childhood due to poor nutrition is associated with an increased risk of stroke in later life.[31] Table 1 shows that for every one SD decrease in the difference between bodyweight at 2 years and that predicted from birthweight, the hazard ratio for stroke in adulthood increased by about 18% (hazard ratio 1·18, 95% CI 1·03–1·28).[31] Continued failure to gain weight during childhood is also associated with an increased risk of stroke in later life; for every one unit SD decrease in weight at different ages during childhood, the hazard ratio for stroke increased by 4–20% (table 2).[31] These data suggest that biological vulnerability to stroke begins during early life and develops throughout the lifespan to increase risk of stroke later in life. This hypothesis is supported by observational data showing a 25% higher incidence of stroke among US adults who had lived as children in the southeastern states, or so-called stroke belt, of the USA, where stroke mortality rates are highest.[34]

Adults

Few data correlate undernutrition in adulthood with risk of stroke. A collaborative analysis of 57 prospective studies in which 894 576 adults were followed up for a mean of 13 years (deaths during the first 5 years were excluded to limit reverse causality) showed that, in the lower range (15–25 kg/m²), each 5 kg/m² lower BMI was associated with a non-significant trend towards an increase in stroke mortality by 9% (hazard ratio 1·09, 95% CI 0·97–1·22).[35] The association was stronger for haemorrhagic stroke (1·32, 1·00–1·72) than for ischaemic stroke (1·15, 0·91–1·47) but was not significant.[35]

Among 8920 individuals with renal impairment who started renal dialysis, undernourishment, low bodyweight, and low serum albumin at baseline were independent, significant predictors of incident stroke after a median follow-up of 3·1 years.[19]

Overnutrition

Obesity is associated with an increased risk of stroke, whether measured by BMI, waist-to-hip ratio, waist-to-height ratio, or waist circumference.[6,17,36–45] Individuals with a BMI of 30 kg/m² or more have double the incidence of ischaemic and haemorrhagic stroke compared with individuals with a BMI of less than

Panel 1: Methods used to establish a causal association between a risk factor and disease

The quality of the evidence used to establish a causal association between a nutritional factor and the risk of stroke is determined by the study design, study quality, consistency, and directness (ie, the extent to which the study participants, interventions, and outcome measures are similar to those of interest).[25,26] The optimal study design is determined by the research question, but each design has its limitations:

Observational cohort or case-control studies

Studies of this type frequently report associations between nutritional factors and stroke risk that are strong, dose-related, independent of other vascular risk factors, and biologically plausible. However, epidemiological studies cannot eliminate bias and confounding in any association between a risk factor and stroke.[27] The association could be due to reverse causality bias (eg, stroke could lead to a change in diet) or residual confounding by other factors, known and unknown, that increase both the risk factor and the risk of stroke (eg, renal impairment). Any association could also be indicative of measurement error in the assessment of nutritional exposures, often at only one or a few points in time, and bias if loss to follow-up occurs.

Meta-analysis of epidemiological studies

Although meta-analyses of multiple epidemiological studies reduce random error (chance) and increase the generalisability (external validity) of the results, they cannot eliminate bias and confounding and have their own limitations. For example, heterogeneity could be introduced by methodological differences between studies, and publication bias could arise if small studies with null results are not published.

Randomised trials

Randomisation is the best method to minimise bias and confounding, and establish causality. However, randomised trials are not always feasible. When they are, the results are also prone to random error if the sample size is inadequate, and are not generalisable beyond the type of participant recruited.

Systematic review and meta-analysis of randomised trials

This method produces the most reliable form of evidence of causality between a nutritional risk factor and the occurrence of stroke. This approach minimises random error and maximises generalisability. However, systematic reviews of randomised trials also have their limitations, including potential for publication bias, study-quality bias, and outcome-recording bias.

	Number of patients	Strokes	Hazard ratio (95% CI)
Weight at 2 years minus predicted weight (kg)			
–1·5 or less	886	50 (5·6%)	1·8 (1·2–2·8)
–1·5 to –0·5	3203	141 (4·4%)	1·4 (0·9–2·0)
–0·5 to 0·5	4693	186 (4·0%)	1·2 (0·8–1·7)
0·5 to 1·5	2600	96 (3·7%)	1·1 (0·8–1·7)
1·5 or more	1056	34 (3·2%)	1·0 (baseline)
Hazard ratio (95% CI) per SD decrease in difference	..	..	1·18 (1·08–1·28)
p for trend	..	..	0·0004

Modified from Osmond and colleagues,[31] by permission of Wolters Kluwer Health.

Table 1: **Association of poor growth in the first 2 years of life with an increased risk of stroke in adulthood**

	Hazard ratio (95% CI) for stroke per one unit SD decrease in weight at different ages
0 years	1·10 (1·01–1·20)
1 years	1·15 (1·05–1·27)
2 years	1·20 (1·10–1·32)
7 years	1·14 (1·03–1·27)
11 years	1·04 (0·94–1·16)

Data from Osmond and colleagues.[31]

Table 2: **Association of low bodyweight at birth, during infancy, and in childhood (poor growth) with an increased risk of stroke in later life**

	Prevalence		Odds ratio (99% CI)	Population attributable risk (99% CI)
	Controls	Cases		
History of hypertension	32%	56%	2·6 (2·3–3·1)	35% (30–39)
No regular physical activity	88%	92%	1·4 (1·1–2·0)	28% (14–48)
Waist-to-hip ratio (tertile 3 *vs* tertile 1)	33%	41%	1·6 (1·4–2·0)	26% (19–36)
Apolipoprotein B to A1 ratio (tertile 3 *vs* tertile 1)	33%	47%	1·9 (1·5–2·4)	25% (16–37)
Current smoking	24%	36%	2·1 (1·7–2·5)	19% (15–23)
Unhealthy diet risk score (tertile 3 *vs* tertile 1)	30%	35%	1·4 (1·1–1·6)	19% (11–30)
Cardiac causes*	5%	12%	2·4 (1·8–3·2)	7% (5–9)
Diabetes	12%	19%	1·4 (1·1–1·7)	5% (3–9)
Depression	14%	20%	1·4 (1·1–1·6)	5% (3–10)
Psychosocial stress	15%	20%	1·3 (1·1–1·6)	5% (2–10)
Alcohol intake >30 drinks per month	11%	16%	1·5 (1·2–1·9)	4% (1–14)

Multivariable model adjusted for age, sex, and region. Risk factors for all stroke in 3000 patients with acute first stroke (within 5 days of symptom onset) compared with 3000 controls with no history of stroke who were matched with cases for age and sex, and who were assessed in 22 countries between 2007 and 2010 in the INTERSTROKE study.[45] Modified from O'Donnell and colleagues,[45] by permission of Elsevier. *Cardiac causes include atrial fibrillation or flutter, previous myocardial infarction, rheumatic valve disease, or prosthetic valve disease.

Table 3: **Risk factors for stroke**

23 kg/m².[37] Each unit increase in BMI is associated with an increase in the adjusted risk of stroke by about 6% (relative risk 6%, 95% CI 4–8).[37] Among adults who are overweight or obese (BMI 25–50 kg/m²), each 5 kg/m² increase in BMI is associated with about 40% higher mortality from stroke (hazard ratio 1·39, 95% CI 1·31–1·48).[35]

Individuals with a waist-to-hip ratio in the highest tertile (>0·96 in men and >0·93 in women) have a 65% increased risk of stroke (odds ratio 1·65, 99% CI 1·36–1·99) compared with individuals in the lowest tertile (<0·91 in men and <0·86 in women).[45] The population attributable risk of stroke associated with an increased waist-to-hip ratio is 26·5% (99% CI 18·8–36·0; table 3).[45]

Although BMI, waist-to-hip ratio, and waist circumference do not meaningfully improve prediction of stroke risk when added to causal risk factors such as systolic blood pressure and history of diabetes, excess adiposity remains a major modifiable determinate of these causal risk factors.[46] Hence, controlling adiposity is likely to help prevent stroke.[5–7,46]

Which nutrients affect the risk of stroke?

Antioxidant vitamins

Many nutrients can affect the risk of stroke (panel 2). The oxidation hypothesis of atherosclerosis—that oxidation of low-density lipoprotein (LDL) cholesterol (lipid peroxidation) allows it to accumulate in artery walls and promote atherosclerosis[81]—prompted several studies of antioxidant vitamins in the prevention of stroke and death.

A meta-analysis of 68 randomised trials of antioxidant supplements versus placebo in 232 605 participants showed that overall, antioxidants had no effect on mortality (relative risk 1·02, 95% CI 0·98–1·06).[47] However, multivariate meta-regression analyses showed that low-bias risk trials (as defined by adequate generation of treatment allocation sequence, allocation concealment, masking, and follow-up) were significantly associated with mortality.[47] In 47 low-bias trials with 180 938 participants, the antioxidant supplements significantly increased mortality (relative risk 1·04, 95% CI 1·02–1·08), especially exposure to vitamin A (1·16, 1·10–1·24), β-carotene (1·07, 1·02–1·11), and vitamin E (1·04, 1·01–1·07); vitamin C (1·06, 0·94–1·20) and selenium (0·90, 0·80–1·02) had no significant effect on mortality.[47]

Vitamin A and β-carotene

β-carotene, the biologically active metabolite of vitamin A, did not affect stroke rates in 82 483 participants enrolled in three randomised trials (odds ratio 1·0, 95% CI 0·91–1·09),[48] but did increase all-cause mortality in 138 113 participants in eight randomised trials (1·07, 1·02–1·11) and cardiovascular mortality among 131 551 participants in six randomised trials (1·10, 1·03–1·17).[48]

Vitamin C

Vitamin C is a water-soluble antioxidant in plasma that helps regenerate oxidised vitamin E. Although observational studies suggest that increased dietary intake and plasma concentrations of vitamin C are associated independently with reduced rates of stroke,[82,83] large randomised trials show no benefit of vitamin C supplementation in preventing stroke and other clinical outcomes.[49–51]

Vitamin E

Vitamin E is a lipid-soluble antioxidant that increases the resistance of LDL cholesterol to oxidation, reduces proliferation of smooth muscle cells, and reduces adhesiveness of platelets to collagen. This vitamin inhibits lipid peroxidation by scavenging reactive oxygen species and preserving cell membranes.[84]

In 2010, a meta-analysis of seven randomised trials with 116 567 individuals revealed that vitamin E had no effect on risk of incident total stroke (relative risk 0·98, 95% CI 0·91–1·05) but increased the risk of incident haemorrhagic stroke (1·22, 1·00–1·48) and reduced the

Panel 2: Effects of nutrients on the risk of stroke

Antioxidant vitamins

Vitamin A

Supplementation increases all-cause mortality.[47]

β-carotene

Supplementation increases cardiovascular and all-cause mortality[47,48] and does not prevent stroke.[48]

Vitamin C

Supplementation does not prevent stroke.[49–51]

Vitamin E

Supplementation increases all-cause mortality[47] and does not prevent stroke.[52]

B vitamins (folic acid)

Supplementation does not prevent stroke in populations with high folate intake;[53] deficiency could be a causal and treatable risk factor for stroke in regions of low folate intake.[54]

Vitamin D

Deficiency is associated with hypertension, cardiovascular disease, and stroke.[55] Supplementation is not proven to prevent cardiovascular events.[56] Randomised trials investigating vitamin D supplementation are in progress.[57]

Salt

Supplementation by 5 g per day is associated with a 23% (95% CI 6–43) increased risk of stroke.[58] Reduction in salt intake is not proven to reduce stroke. Reduction by 2 g per day reduces cardiovascular events by 20% (95% CI 1–36);[59,60] reduction also lowers blood pressure.[61–65]

Potassium

Supplementation by 1 g per day is associated with an 11% (95% CI 3–17) reduction in the risk of stroke; [66] supplementation is not proven to prevent stroke. Supplementation by 0·8 g per day reduces blood pressure by 5/3 mm Hg.[67,68]

Calcium

Supplementation by more than 0·5 g per day does not prevent stroke, might increase the risk of stroke,[69,70] and can increase the risk of myocardial infarction by 31% (95% CI 2–67).[69]

Fats

Total fat

High intake is not associated with increased risk of stroke.[71]
Reduced intake does not reduce risk of stroke.[72]

Trans fats

High intake is not associated with increased risk of stroke.[71]

Saturated fats

High intake is not associated with increased risk of stroke.[71,73]

Marine n-3 polyunsaturated fats

Supplementation reduces cardiovascular events and death by 8% (95% CI 1–15),[74] but in one randomised trial it did not reduce stroke risk (hazard ratio 1·04, 95% CI 0·62–1·75).[75]

Plant n-3 polyunsaturated fats

High intake is associated with reduced risk of stroke.[76]

Carbohydrates

High glycaemic index and glycaemic load

High intake of food with these nutritional qualities is associated with increased blood glucose and bodyweight.[77] High intake is associated with increased stroke mortality.[78]

Fibre

High intake is associated with reduced blood pressure, blood glucose, and LDL-cholesterol.[79]

Proteins

High intake is not associated with risk of stroke.[80]

risk of incident ischaemic stroke (0·90, 0·82–0·99).[85] Heterogeneity among the studies was not evident (I^2=12·8%; p for heterogeneity=0·33). However, in 2011, an updated meta-analysis of 13 randomised trials of vitamin E in 166 282 participants showed no significant benefit in the prevention of stroke of any type (relative risk 1·01, 95% CI 0·96–1·07), ischaemic stroke (1·01, 0·94–1·09), or haemorrhagic stroke (1·12, 0·94–1·33).[52] Significant heterogeneity among the studies was not evident (p for heterogeneity=0·37).

The reasons for the discrepancy in findings for the effect of vitamin E on the pathological subtypes of stroke in the two meta-analyses[52,85] might be the inclusion of six additional trials, longer follow-up data from one shared trial, and perhaps (although not stated) recurrent as well as incident strokes in the updated meta-analysis.[52]

B vitamins

Increased serum concentrations of total homocysteine have been associated independently with an increased risk of all types of stroke combined, and ischaemic stroke due to large artery disease, small artery disease, and embolism from the heart in observational studies.[86–89] Although homocysteine can be lowered by up to 25% (95% CI 22–28) with folic acid and by a further 7% (4–9) with vitamin B12 (median dose 0·4 mg [range 0·4–1·0] per day),[90] randomised trials of folic acid versus control showed no effect of supplementation with folic acid on all stroke (relative risk 0·96, 95% CI 0·87–1·06).[53] The results of genetic epidemiological studies are concordant with those from randomised trials in populations with established or increasing folate intake but, in populations with low folate intake (eg, Asia), the genetic studies suggest that lowering total homocysteine by 3·8 μmol/L could reduce stroke by 22% (95% CI 10–32).[54] Because no large, reliable randomised trials of total homocysteine reduction in regions of low folate intake have been done, whether supplementing the diet or fortifying food with folic acid in these regions could reduce stroke incidence is not known.

In individuals who are folate-replete, vitamin B12 is an important determinant of total homocysteine, and subclinical vitamin B12 deficiency is not uncommon.[91] Subgroup analyses from randomised trials raise the hypothesis that use of high doses of vitamin B12 in people who are folate-replete but vitamin B12 deficient could substantially lower total homocysteine and risk of stroke.[91–94] This hypothesis requires confirmation a priori in clinical trials.

Vitamin D

Observational studies report an association between deficiency of 25-hydroxyvitamin D and an increased incidence of hypertension, carotid artery atherosclerosis, and cardiovascular disease, including stroke.[55,95] Although randomised trials show that vitamin D supplementation lowers blood pressure[55] and improves endothelial function in the short term,[96] two trials showed no significant effect on cardiovascular events of vitamin D supplementation at moderate to high doses (relative risk 0·90, 95% CI 0·77–1·05) or of vitamin D plus calcium supplementation (1·04, 0·92–1·18).[56]

For more on **the VITAL study** see http://www.vitalstudy.org

The VITamin D and OmegA-3 triaL (VITAL) is currently randomly assigning 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.[57] 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).[57]

Minerals

An observational study of 38 772 older women (mean age 61·6 years in 1986) reported that subsequent mortality was increased significantly in users of multivitamins (hazard ratio 1·06, 95% CI 1·02–1·10; absolute risk increase 2·4%), folic acid (1·15, 1·00–1·32; 5·9%), vitamin B6 (1·10, 1·01–1·21; 4·1%), iron (1·10, 1·03–1·17; 3·9%), magnesium (1·08, 1·01–1·15; 3·6%), zinc (1·08, 1·01–1·15; 3·0%), and copper (1·45, 1·20–1·75; 18·0%), and decreased in users of calcium (0·91, 0·88–0·94; 3·8%).[97] These results and the effects on risk of stroke and its subtypes require confirmation by randomised trials.

Salt

Most adult populations around the world have average daily salt intakes of higher than 6 g, and many in eastern Europe and Asia of more than 12 g, mostly from processed foods.[58] Observational studies show that sustained high daily salt intake of 5 g on average (86 mmol [one teaspoon]) is associated with a 23% greater risk of stroke (pooled relative risk 1·23, 95% CI 1·06–1·43) and a 17% greater rate of total cardiovascular disease (relative risk 1·17, 1·02–1·34).[58] No data on stroke subtypes were available but a large prospective, community-based, case-control study reported that adding salt to food not only independently increased the odds of all stroke (odds ratio 1·5, 95% CI 1·0–2·3), but that most of the effect was driven by an increase in odds of haemorrhagic stroke (3·5, 95% CI 1·6–7·6).[98] Indeed, about 20% (95% CI 1–38) of all primary intracerebral haemorrhages were attributable to adding salt to food.[98]

A meta-analysis of six randomised trials showed that a reduction in dietary salt intake by 2·0–2·3 g (half a teaspoon) per day was associated with a reduction in cardiovascular events by 20% (relative risk 0·80, 95% CI 0·64–0·99).[59,60] However, no randomised trials of the effect of salt reduction on risk of stroke or its pathological and aetiological subtypes have been done.

Excess salt intake might increase cardiovascular and stroke risk by increasing blood pressure and causing fibrosis in the heart, kidneys, and arteries.[99] Reducing dietary salt intake by 6 g a day reduces systolic and diastolic blood pressure by 4 and 2 mm Hg, respectively, in people without hypertension, 7 and 4 mm Hg, respectively, in those with hypertension,[100,101] and 23 and 9 mm Hg, respectively, in people with resistant hypertension.[61] Sodium reduction by 6 g per day also blunts the age-related rise in blood pressure by about 0·5 mm Hg per year.[62,63] The response of blood pressure to sodium reduction is direct and progressive, but non-linear; decreasing sodium intake by about 0·9 g per day causes a greater reduction in blood pressure when the starting sodium intake is about 2·3 g per day than when it is about 3·5 g per day.[64,65]

Potassium

A higher potassium intake of 42 mmol/L (1·64 g) per day was associated with a 21% reduced risk of stroke after 5–19 years of follow-up of 247 510 adults in 11 observational studies (relative risk 0·79, 95% CI 0·60–0·90).[102] For every increase in potassium intake by 1·0 g per day, the risk of stroke decreased by 11% (relative risk 0·89, 95% CI 0·83–0·97).[66] If causal, the association might be mediated by lowered blood pressure; increasing potassium intake by 20 mmol (0·78 g) or more per day lowers blood pressure by an average of 4·9 mm Hg systolic blood pressure and 2·7 mm Hg diastolic blood pressure in patients with hypertension.[67,68] Randomised trials are needed to establish the independent effects of long-term increases in dietary potassium intake on stroke risk, but are unlikely to be undertaken because of technical difficulties and possible ethical constraints.

Calcium

Many guidelines recommend adequate calcium intake as part of the prevention or treatment of osteoporosis,[103] despite the fact that calcium supplements only marginally reduce the risk of fracture.[104] Interventional studies show that calcium supplements improve some risk factors for stroke such as blood pressure,[105,106] bodyweight,[106] and serum-lipid concentrations,[107] and observational studies

suggest that high calcium intake might protect against stroke.[108,109] However, a recent observational study of 34 670 women reported that increasing calcium intake was not associated with altered risk of any stroke or ischaemic stroke, but was associated with an increased risk of haemorrhagic stroke (for highest *vs* lowest tertile; adjusted relative risk 2·04, 95% CI 1·24–3·35).[110] Randomised trials have shown that, after a median of 3·6 years (IQR 2·7–4·3), calcium supplementation (≥500 mg per day), without co-administered vitamin D, is associated with a significant increase in myocardial infarction (hazard ratio 1·31, 1·02–1·67) and a trend towards an increase in stroke (1·20, 0·96–1·50).[69]

Co-administration of calcium plus vitamin D supplements for an average of 6·2 years was associated with an increased risk of stroke (relative risk 1·20, 95% CI 1·00–1·43), myocardial infarction (1·21, 1·01–1·44), and the composite of myocardial infarction or stroke (1·16, 1·02–1·32) among 20 090 individuals in three placebo-controlled trials.[70]

Some studies do not distinguish between calcium taken alone and calcium co-administered with vitamin D. An analysis of such studies showed that calcium alone or calcium plus vitamin D increased the risk of stroke (hazard ratio 1·19, 95% CI 1·02–1·39), myocardial infarction (1·26, 1·07–1·47), and the composite of stroke or myocardial infarction (1·17, 1·05–1·31) over a mean follow-up of 5·9 years in 24 869 people in six randomised trials.[70] These data suggest that treating 1000 people with calcium or calcium and vitamin D for 5 years would cause an additional six myocardial infarctions or strokes and prevent three fractures. However, methodological caveats exist that limit the conclusiveness of this evidence. Furthermore, when calcium and vitamin D supplements are used as an adjunct to bisphosphonates in the treatment of osteoporosis, no adverse effect on cardiovascular safety and survival occurs.[111,112] Randomised trials of the effects of calcium, with or without vitamin D, on the risk of stroke, its pathological and aetiological subtypes, and other vascular and non-vascular outcomes are warranted.

Fats

An observational study of 43 732 men in the USA showed that, compared with the lowest quintile, the risk of ischaemic stroke over 14 years of follow-up was not increased in those in the highest quintile for intake of total fat (adjusted relative risk 0·91, 95% CI 0·65–1·28; p for trend 0·77), animal fat (1·20, 0·84–1·70; p for trend 0·47), saturated fat (1·16, 0·81–1·65; p for trend 0·59), vegetable fat (1·07, 0·77–1·47; p for trend 0·66), dietary cholesterol (1·02, 0·75–1·39; p for trend 0·99), monosaturated fat (0·88, 0·64–1·21; p for trend 0·25), or transunsaturated fat (0·87, 0·62–1·22; p for trend 0·42).[71] These findings are supported by a large randomised trial in which a reduction of mean total fat intake by 8·2% of energy intake over 8·1 years (mean) did not significantly reduce the risk of stroke (hazard ratio 1·02, 95% CI 0·90–1·15) in 48 835 postmenopausal women.[72] However, trends towards greater reductions in risk of coronary heart disease were seen with low intakes of trans fat and saturated fat,[72] suggesting that the type of fats consumed might be more relevant for cardiometabolic health than the proportion of calories consumed from total fat.[113,114]

Trans fatty acids

Consumption of industrially produced trans fatty acids from partially hydrogenated vegetable oils are the most potent fat-related risk factor for coronary heart disease.[115,116] Although observational studies suggest no significant relation between trans fat consumption and risk of stroke,[71] no reliable observational data or data from randomised trials on the association of trans fatty acids with stroke subtypes are available.

Saturated fatty acids

A meta-analysis of eight observational studies showed that intake of saturated fat in the highest quintile was not associated with an increased risk of stroke compared with intake in the lowest quintile (relative risk 0·81, 95% CI 0·62–1·05).[73] Sufficient statistical power in these studies was not available to assess whether the observed associations between saturated fat intake and stroke risk were modified or confounded by the cardiometabolic effects of nutrients, such as refined carbohydrates, starches, and sugars, which might be exchanged for saturated fatty acids.[113,117] Data on the relation between saturated fat intake and risk of subtypes of stroke were also restricted.

Polyunsaturated fatty acids

No reliable studies of the association between increased intake of polyunsaturated fatty acids and stroke risk have been done, but observational studies and randomised trials suggest that consumption of these fatty acids in place of saturated fatty acids reduces incidence of coronary heart disease.[113,118] For each 5% of energy obtained from polyunsaturated fatty acids, instead of saturated fatty acids, the risk of coronary heart disease is reduced by 10% (relative risk 0·90, 95% CI 0·83–0·97).[118]

Marine-derived omega-3 (or n-3) polyunsaturated fatty acids

Human beings rely on direct dietary consumption of omega-3 polyunsaturated fatty acids, which include eicosapentaenoic acid (20:5 omega-3) and decosahexaenoic acid (22:6 omega-3) from oily fish such as salmon, herring, trout, and sardines.[113]

A meta-analysis of 11 randomised trials including 39 044 patients showed that random allocation to the omega-3 fatty acids eicosapentaenoic acid or decosahexaenoic acid for 2·2 years (mean) significantly reduced cardiovascular deaths (odds ratio 0·87, 95% CI 0·79–0·95), sudden cardiac death (0·87, 0·76–0·99), all-cause mortality (0·92, 0·85–0·99), and non-fatal cardiovascular events (0·92, 0·85–0·99) compared with

placebo.[74] The effect could be mediated by an anti-arrhythmic effect or other beneficial effects on blood pressure, concentration of plasma triglycerides, and markers of thrombosis and inflammation.[119]

However, a subsequent randomised trial showed that in 2501 patients with a history of myocardial infarction, unstable angina, or ischaemic stroke, random assignment to a daily dietary supplement containing omega-3 fatty acids (600 mg of eicosapentaenoic acid and decosahexaenoic acid at a ratio of 2:1) for a median of 4·7 years had no significant effect on stroke (hazard ratio 1·04, 95 CI% 0·62–1·75) or major vascular events (1·08, 0·79–1·47).[75] The effect of treatment on stroke subtypes was not reported.

Plant-derived omega-3 (n-3) polyunsaturated fatty acids

The plant-derived n-3 polyunsaturated fatty acid α-linolenic acid is an essential fatty acid found mainly in vegetable oils such as soybean, canola, and flaxseed, and in walnuts. An observational study of 20 069 Dutch adults showed that, compared with the bottom quintile (Q1) of α-linolenic acid intake (less than 1·0 g per day), participants in high quintiles (Q2–Q5) had a 35–50% lower risk of incident stroke; hazard ratios were 0·65 (0·43–0·97; Q2), 0·49 (0·31–0·76; Q3), 0·53 (0·34–0·83; Q4), and 0·65 (0·41–1·04; Q5) after 8–13 years of follow-up.[76] These results need confirmation in randomised trials.

Carbohydrates

Like fat intake, carbohydrate intake in quantities that exceed energy requirements (positive energy imbalance) is a major determinant of weight gain and adiposity,[113] and the quality of carbohydrate intake also affects metabolic health. Consumption of refined sugars in liquid form promotes weight gain.[113] The glycaemic index is a measure of how much a standard quantity of food raises blood glucose levels compared with a standard quantity of glucose or white bread. The glycaemic load is a measure of the product of the glycaemic index of a food item and the available carbohydrate content of that item. Foods with a high glycaemic index, such as sugar-sweetened beverages and refined carbohydrates and starches, increase fasting blood glucose. Glycated proteins, and beverages and foods with high glycaemic load, including added sugars, increase bodyweight.[77] High carbohydrate intake from foods with a high glycaemic index, added sugars, and high dietary glycaemic load also leads to reduced intake of essential nutrients and has been associated with an increased risk of stroke mortality and coronary heart disease in women in observational studies.[78,120,121] Replacement of saturated fats with carbohydrates that have a high glycaemic index is associated with an increased risk of myocardial infarction (hazard ratio for myocardial infarction per 5% increment of energy intake of carbohydrates 1·33, 95% CI 1·08–1·64).[122]

Increased dietary fibre reduces blood pressure, blood glucose, serum triglycerides, and LDL cholesterol[79] but no reliable data on its effect on risk of stroke and stroke subtypes are available.

Protein

Observational studies in Japan have shown that increased protein intake is associated with reduced risk of stroke.[123] However, no significant association between total, animal, or vegetable protein and risk of stroke was reported in a cohort study of 43 960 men in the USA.[80]

Which foods and beverages affect the risk of stroke?

Many foods and beverages affect the risk of stroke (panel 3). The INTERSTROKE study[45] reported that, within food groupings (adjusted for age, sex, and region; tertile 3 *vs* tertile 1), increased consumption of fish (odds ratio 0·78, 99% CI 0·66–0·91) and fruit (0·61, 0·50–0·73) were associated with reduced risk of stroke.[45]

Fish

Fish can be an excellent source of protein and the essential omega-3 fatty acids eicosapentaenoic acid and decosahexaenoic acid. A meta-analysis of 15 observational studies reported that an increase in consumption of three servings per week of fish was associated with a 6% (95% CI 1–11) lower risk of stroke.[124] No significant heterogeneity among the studies was reported (I^2=25·7%).[124] Some studies suggest that consumption of oily fish drives the inverse association between fish intake and stroke risk[139,140] and others suggest that the consumption of lean fish (cod, saithe, and fish fingers), but not other fish types (eg, salmon, white fish, and char, herring, or mackerel), is associated with a lower risk of stroke.[141] The effect of the consumption of lean fish could be confounded by the fact that herring and salmon are commonly eaten salted in Sweden, thus affecting blood pressure levels.

Studies that have examined pathological subtypes of stroke suggest that fish consumption is associated with a lower risk of ischaemic stroke but not haemorrhagic stroke.[142] However, no reliable data from randomised trials of the effect of fish consumption on the risk of stroke or its subtypes are available.[143–145]

Fruit and vegetables

Increased fruit and vegetable intake (more than five servings per day) was associated with a lower risk of stroke than was intake of fewer than three servings per day (relative risk 0·74, 95% CI 0·69–0·79) and three to five servings per day (0·89, 0·83–0·97) in 257 551 individuals followed up for 13 years.[125] However, vegetable intake alone was not associated with a reduced risk of stroke (odds ratio 0·91, 99% CI 0·75–1·10) in the INTERSTROKE study.[45] If the association between fruit and vegetable intake is validated, the mechanism might be that consumption of

five or more daily portions of fruit and vegetables reduces blood pressure by about 4·0 mm Hg (95% CI 2·0–6·0) systolic and 1·5 mm Hg (0·2–2·7) diastolic.[126]

Meats

A meta-analysis of observational studies including 152 630 individuals showed that total meat consumption was associated with a 24% higher risk of ischaemic stroke per daily serving (relative risk 1·24, 95% CI 1·08–1·43).[127] Among subtypes of meat, consumption of unprocessed red meats (which contain saturated fatty acids, cholesterol, and haem iron[113]) was not associated with a significant increase in risk of ischaemic stroke or total stroke mortality (relative risk per 100 g serving per day 1·17, 95% CI, 0·40–3·43) and nor was intake of processed meats (which contain high levels of salt and other preservatives;[113] relative risk 1·14, 95% CI, 0·94–1·39).[127] However, a recent large cohort study of 40 291 men reported that processed meat consumption was positively associated with an increased risk of stroke (multivariate relative risk for highest *vs* lowest quintiles 1·23, 95% CI 1·07 to 1·40) after a mean follow-up of 10·1 years.[128] Further studies of meat consumption by subtype and risk of stroke by pathological and aetiological subtypes are needed.

Dairy

The dairy products milk, cheese, and butter have a high saturated fat and calcium content that could increase the risk of stroke. However, a meta-analysis of six cohort studies showed that milk intake was not associated with risk of stroke (relative risk 0·87, 95% CI 0·72–1·05).[129] A subsequent large cohort study reported that dairy fat intake was associated with slightly increased all-cause mortality in women (per 10 g per day; rate ratio 1·04, 95% CI 1·01–1·06) and fermented milk was associated with a possible protective effect against stroke mortality.[146] Case-control studies suggest that consumption of reduced-fat or skimmed milk, compared with full-strength milk, is associated with reduced odds of all stroke (odds ratio 0·49, 95% CI 0·31–0·76) and ischaemic stroke (0·43, 0·26–0·72).[98]

Chocolate

Observational studies suggest that individuals with the highest levels of chocolate consumption have a 29% (95% CI 2–48) lower rate of stroke and 37% (10–56) lower rate of cardiovascular disease than those with the lowest levels of chocolate consumption.[130] If valid, the mechanism of this association might include antihypertensive, anti-inflammatory, antiatherogenic, and antithrombotic effects of cocoa.[130]

Coffee

A meta-analysis of 11 prospective studies of 479 689 participants in which three or more categories of coffee consumption were correlated with the subsequent occurrence of 10 003 cases of stroke reported that moderate coffee consumption might have a weak non-linear inverse association with risk of stroke (p for non-linearity=0·005).[131] Compared with no coffee consumption, the relative risks of stroke were 0·86 (95% CI 0·78–0·94) for two cups of coffee per day, 0·83 (0·74–0·92) for three to four cups per day, 0·87 (0·77–0·97) for six cups per day, and 0·93 (0·79–1·08) for eight cups per day. Marginal between-study heterogeneity was present.[131]

Panel 3: Effects of foods and beverages on the risk of stroke

Fish

Increased consumption by three servings per day is associated with a 6% (95% CI 1–11) lower risk of stroke.[124]

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.[125] Consumption of more than five servings per day lowers blood pressure by 4·0/1·5 mm Hg.[126]

Meat

Total meat

Each daily serving is associated with a 24% (95% CI 8–43) increased risk of stroke.[127]

Unprocessed meat

Consumption is not a proven risk factor for stroke.[127]

Processed meat

Consumption was associated with an increased risk of stroke in one observational study[128] but not in another.[127]

Dairy

Milk

Consumption is not associated with risk of stroke.[129]

Reduced-fat milk (vs full-strength milk)

Consumption is associated with lower risk of stroke.[98]

Chocolate

High consumption is associated with a 29% (95% CI 2–48) lower risk of stroke.[130]

Coffee

Moderate consumption (3–4 cups per day) is associated with a 17% (95% CI 8–26) lower risk of stroke.[131,132]

Tea

Moderate consumption (≥3 cups per day) is associated with a 21% (95% CI 15–27) lower risk of stroke.[133]

Sugar-sweetened beverages

High intake is associated with increased obesity, diabetes, metabolic syndrome, and coronary heart disease.[134-136]

Whole grains

High intake is associated with a 21% (95% CI 15–27) lower incidence of cardiovascular events.[137]

Rice

Intake is not associated with risk of stroke.[138]

The association between coffee consumption and pathological subtype of stroke was examined in a single cohort study of 34 670 women, which reported that, after a mean follow-up of 10·4 years, consumption of at least one cup of coffee a day was associated with a lower risk of ischaemic stroke and subarachnoid haemorrhage but not haemorrhagic stroke compared with consumption of less than one cup of coffee a day.[132]

This association, if causal, is unlikely to be mediated by blood pressure because caffeine intake is not associated with a long-term increase in blood pressure compared with a caffeine-free diet or with decaffeinated coffee, despite the fact that caffeine intake of 200–300 mg produces an acute mean increase in blood pressure of 8·1 mm Hg (95% CI 5·7–10·6) systolic and 5·7 mm Hg (95% CI 4·1–7·4) diastolic for 3 h or more.[147] The effect could be due to the action of the phenolic compounds in coffee, which might increase resistance of LDL cholesterol to oxidation.[131]

Although chronic coffee consumption is associated with a lower risk of stroke,[131,132] some preliminary evidence suggests an acutely increased risk of ischaemic stroke in the hour after coffee intake (relative risk 2·0, 95% CI 1·4 to 2·8), especially in infrequent coffee drinkers (one cup or less a day).[148] Because these results could mirror recall bias, they require confirmation.

Tea

A meta-analysis of nine observational studies of 194 965 individuals reported that consumption of three or more cups of tea (green or black) a day was associated with a 21% (95% CI 15–27%) lower risk of stroke than in those who consumed less than one cup a day (I^2=23·8%).[133] Population-based studies do not suggest that tea lowers blood pressure,[149] but it might have a favourable effect on endothelial function and reduce the oxidation of LDL cholesterol.[150,151]

Sugar-sweetened beverages

High intake of sugar-sweetened beverages leads to lower intake of more healthy beverages and is associated with adiposity, and an increased incidence of diabetes mellitus, metabolic syndrome, and coronary heart disease.[134–136] However, no reliable data exist that relate intake of sugar-sweetened beverages to incidence of stroke.

Whole grains

Whole grains comprise bran, germ, and endosperm from natural cereal.[113] Bran contains soluble and insoluble dietary fibre, B vitamins, minerals, flavonoids, and tocopherols; germ contains many fatty acids, antioxidants, and phytochemicals; and endosperm provides largely starch (carbohydrate polysaccharides) and storage proteins.[113] Consumption of whole grains improves glucose-insulin homoeostasis and endothelial function, and possibly reduces inflammation and improves weight loss.[137]

Increased whole grain intake (pooled average 2·5 servings a day *vs* 0·2 servings a day) was associated with a trend towards a lower risk of incident stroke events (odds ratio 0·83, 95% CI 0·68–1·02) and a significantly lower risk of cardiovascular disease events (0·79, 0·73–0·85) in seven observational studies whereas refined grain intake was not associated with incident cardiovascular disease events (1·07, 0·94–1·22).[137]

Rice

Rice intake was not associated with risk of stroke (adjusted hazard ratio per one SD increment of energy-adjusted risk intake 0·97, 95% CI 0·90–1·04) in a study that followed 83 752 Japanese adults for a median of 14·1 years.[138]

Legumes

Legumes include beans, peas, chickpeas, and lentils; their independent effects on risk of stroke are unknown. However, randomised trials have shown that soy-containing foods produce a non-significant reduction in blood pressure by about 5·8 mm Hg systolic and 4·0 mm Hg diastolic,[152] and isolated soy protein or isoflavones (phytoestrogens) lower diastolic blood pressure by 2 mm Hg and LDL cholesterol by 3%.[153]

Which dietary patterns affect the risk of stroke?

Dietary patterns can have various effects on risk of stroke (panel 4). Several studies have developed and assessed diet scores as a risk factor for stroke, often in conjunction with other lifestyle factors.[45,154–156]

Healthy versus unhealthy diets

In the Women's Health Study of 37 636 women aged 45 years or older, a healthy diet was defined as one high in cereal fibre, folate, and omega-3 fatty acids, with a high ratio of polyunsaturated to saturated fat, and low in trans fats and glycaemic load, but was unexpectedly associated with an increased risk of stroke over 10 years of follow-up.[154]

In the Nurses' Health Study of 71 243 women and the Health Professionals Follow-Up Study of 43 685 men, a score within the top 40% of a healthy diet score (as defined by high intakes of fruits, vegetables, soy, nuts, and cereal fibre; a high ratio of polyunsaturated to saturated fat and chicken plus fish to red meat; low intake of trans fats; and use of multivitamins for ≥5 years) was associated with a trend towards a lower risk of stroke in men (relative risk 0·90, 95% CI 0·80–1·00) but not in women (1·10, 0·89–1·16).[155]

The INTERSTROKE study[45] identified an unhealthy diet as a significant risk factor for stroke (table 3). An unhealthy diet risk score was derived from a simple 19-item qualitative food-group-frequency questionnaire about consumption of meat, salty snacks, fried foods, fruits, green leafy vegetables, cooked vegetables, and other raw vegetables (a high score indicating a poorer

[increasingly unhealthy cardiovascular] diet). Compared with the lowest (first) quartile, the odds ratio of stroke in the highest (third) tertile was 1·35 (99% CI 1·11–1·64). The adjusted population-attributable risk of stroke for the top two tertiles compared with the bottom quartile of the dietary risk score was 18·8% (99% CI 11·2–29·7).[45]

Prudent versus western diets

A prudent diet, characterised by high intakes of fruits, vegetables, legumes, fish, and whole grains, was associated with a lower risk of stroke after 14 years of follow-up of 71768 women (relative risk 0·78, 95% CI 0·61–1·01; comparing extreme quintiles) whereas a western diet, characterised by high intakes of red and processed meats, refined grains, and sweets and desserts, was associated with an increased risk of stroke (relative risk 1·58, 95% CI 1·15–2·15; comparing the highest with lowest quintiles of the western diet).[156]

DASH-style diets

The Dietary Approaches to Stop Hypertension (DASH) diet contains a high intake of plant foods, fruits and vegetables, fish, poultry, whole grains, low-fat dairy products, and nuts, while minimising intake of red meat, sodium, sweets, and sugar-sweetened beverages.

Adherence to the DASH-style diet was associated with a lower risk of stroke during 24 years of follow-up of 88 517 middle-aged women (aged 34–59 years; multivariate relative risk across quintiles of the DASH score were 1·0 [reference; Q1], 0·92 [95% CI 0·81–1·05; Q2], 0·91 [0·80–1·03; Q3], 0·89 [0·78–1·02; Q4], and 0·82 [0·71–0·94; Q5]; p=0·002 for trend).[157] The DASH diet lowers blood pressure and improves blood lipids compared with typical western diets,[161] which might explain this association, if valid.

Mediterranean diets

The Mediterranean diet is a collection of eating habits traditionally followed by people in the different countries bordering the Mediterranean Sea. This diet is characterised by a high consumption of fruit, vegetables, legumes, and complex carbohydrates (whole grains); a moderate consumption of fish; consumption of olive oil as the main source of fats (monounsaturated); a low-to-moderate amount of red wine during meals; and low consumption of red meat, refined grains, and sweets.

A meta-analysis of 18 observational studies involving 2 190 627 people showed that a two-point increase in adherence to the Mediterranean diet was associated with a significant reduction of overall mortality (relative risk 0·92, 95% CI 0·90–0·94) and cardiovascular incidence or mortality (0·90, 0·87–0·93) over 4–20 years of follow-up.[160] One study examined the effect of the Mediterranean diet on stroke in 74 886 women over the following 20 years and reported that those with the greatest adherence to the Mediterranean diet—in the top quintile of the alternate Mediterranean diet score—were at lower risk of stroke than those in the bottom quintile (relative risk 0·87, 95% CI 0·73–1·02; p for trend 0·03).[158] The protective effect of the Mediterranean diet on stroke risk has also been reported in case-control studies.[159]

The Mediterranean diet is more effective than a low-fat diet in reducing oxidised LDL concentrations and blood pressure[162,163] and, in obese individuals, improving weight loss and lowering the ratio of total to high-density lipoprotein cholesterol.[164]

Vegetarian diets

Compared with typical western diets, vegetarian diets can reduce blood pressure[165] but lactovegetarian (milk consumed) and vegan (no animal products consumed) diets have not been shown to reduce blood pressure, bodyweight, concentrations of blood lipids, or insulin resistance.[113,166]

Vegetarians might have improved survival compared with non-vegetarians[167] but, if so, whether it is because the components of the diet (plant-based foods) replace unhealthy processed meats and other processed and fast foods or whether the diet is a marker of individuals (vegetarians) who might be more health conscious in other aspects of their lifestyle behaviours is unclear.

***Panel 4*: Effects of dietary patterns on the risk of stroke**

Healthy diet
High intake of a healthy diet was associated with an increased risk of stroke in one observational study[154] and a reduced risk of stroke in another observational study[155]

Unhealthy diet
High intake of an unhealthy diet is associated with an increased risk of stroke[45] and a population-attributable risk of stroke of 19% (99% CI 11–30)[45]

Prudent diet
In women, high intake of a prudent diet is associated with a lower risk of stroke than is low intake[156]

Western diet
In women, high intake of a western diet is associated with a higher risk of stroke than is low intake[156]

DASH-style diet
In women, high intake of a DASH-style diet is associated with a lower risk of stroke than is low intake[157]

Mediterranean diet
In women, high intake of a Mediterranean diet is associated with a lower risk of stroke,[158,159] cardiovascular disease, cardiovascular mortality, and all-cause mortality[160] than is low intake

Vegetarian diet
Effect on stroke risk is not known

Japanese diet
Effect on stroke risk is not known

DASH=Dietary Approaches to Stop Hypertension.

Search strategy and selection criteria

I searched PubMed articles published from 1970 to October, 2011, using the search terms "stroke", "nutrition", "undernutrition", "overnutrition", "nutrients", "foods", "diet", "dietary patterns", "overweight", "obesity", "mortality", "prospective cohort studies", "randomized controlled trial(s)", "systematic review", and "meta-analysis". Articles were also identified through searches of reference lists and my own files. Studies were selected for inclusion on the basis of a judgment about the quality of the evidence according to four key elements: study design, study quality, consistency, and directness (ie, the extent to which the study participants, interventions, and outcome measures are similar to those of interest), as proposed by the Grading of Recommendations Assessment, Development and Evaluating (GRADE) working group. For each nutrient, food, or dietary pattern, only the studies with the highest level of evidence were included. If randomised trials had not been undertaken and only observational data were available, studies were included if they were prospective, population-based, and large, with standardised diagnostic criteria for stroke outcome events (and, ideally, also pathological and aetiological stroke subtypes), prolonged follow-up, and statistical adjustment for the effect of other potential prognostic variables by means of multiple regression analysis. Studies were excluded if serious limitations to study quality and major uncertainty about directness existed. Only articles published in English were included.

For more on **the GRADE working group** see http://www.gradeworkinggroup.org/

Japanese diets

Traditional Japanese diets, characterised by increased intake of fish, plant foods (soybean products, seaweeds, vegetables, fruits), and sodium (soy sauce and added salt), decreased intake of refined carbohydrates and animal fat (meats), and appropriate energy balance have been associated in ecological studies with some of the lowest rates of coronary heart disease in the world.[123,168–171] In observational cohort studies, the Japanese dietary pattern has also been associated with a reduced risk of cardiovascular mortality (hazard ratio for the highest *vs* lowest quartile 0·73, 95% CI 0·59–0·90).[172]

However, the rates of stroke in Japan remain high, perhaps because of the greater relevance of hypertension to stroke than coronary heart disease, and the effect of the high sodium diet and, for men, high alcohol consumption in the Japanese population. By contrast, low saturated fat (meat) and high n3-polyunsaturated fat (fish) in the Japanese diet could contribute to the low prevalence of hypercholesterolaemia, which is more relevant to risk of coronary heart disease than to stroke.[173]

Conclusions and future directions

Many studies have assessed the associations between dietary exposures and stroke risk. The findings are diverse, mainly because most studies are epidemiological and prone to substantial methodological challenges of bias, confounding, and measurement error. Furthermore, most studies have classed stroke as a composite outcome, without distinguishing first-ever stroke from recurrent stroke, ischaemic stroke from haemorrhagic stroke (pathological stroke subtypes), ischaemic stroke due to large artery disease from that due to small artery disease and embolism from the heart (aetiological subtypes of ischaemic stroke), and haemorrhagic stroke due to hypertensive small vessel disease from its many other causes. Consequently, important potential effects of nutrients, foods, beverages, and dietary patterns on specific pathophysiological mechanisms of one stroke subtype could have been diluted and missed by assessing a single outcome of stroke. The same applies to nutritional factors; overall negative associations between total fat or total carbohydrate intake and stroke risk could mask important associations between specific subtypes of fat and subtypes of carbohydrate intake that influence health and stroke risk. These limitations have led one commentator to lament: "almost every nutritional 'fact' is in reality an opinion, often based on poor quality evidence."[174]

However, the few randomised trials that have been undertaken provide more reliable conclusions than do previous epidemiological studies—that dietary supplementation with antioxidant vitamins, B vitamins, and calcium do not reduce the risk of stroke. Indeed, calcium might increase myocardial infarction, and β-carotene, vitamin A, and vitamin E might increase mortality. Less reliable observational data suggest that a lower risk of stroke could be associated with diets that are low in salt and added sugars, high in potassium, and contain the ingredients of a Mediterranean diet. The overall quality of an individual's diet (ie, dietary pattern) and balance between energy intake and expenditure seem to be more important determinants of stroke risk than individual nutrients and foods.

Further research is needed to improve the quality of evidence relating to the association of many nutrients, foods, and dietary patterns with stroke risk. To establish a causative role for specific nutrients, foods, and dietary patterns in the pathogenesis of stroke, adequately powered, large randomised trials are needed in which the patient population and intervention are carefully described and the outcomes not only include all stroke but also distinguish first-ever and recurrent stroke, and pathological and aetiological subtypes of stroke. A large randomised trial is currently examining the effect of vitamin D and marine omega-3 fatty acid supplementation on incidence of stroke.[57] To examine the effects of interactions between different genetic and environmental factors, large genetic epidemiological studies that minimise bias, confounding, measurement error, and random error are needed.

At a population level, the two main nutritional threats to global health and risk of stroke are over-consumption of calories and salt. These behaviours are a normal response by people to an abnormal environment.[5] Our living environments have become more conducive to consumption of energy and less conducive to expenditure of energy in developed and increasingly in developing regions. Most of the salt in our diet is added to food before it is sold. If the environment is not changed to increase energy expenditure and to supply healthy food in appropriate, affordable, and accessible quantities, the obesity epidemic will not be reversed and, by 2050, 60% of

men and 50% of women in the UK could be clinically obese.[175] Unlike the tobacco and cardiovascular disease epidemic, the obesity and salt epidemics have not been reversed by public health interventions and policies aimed at individuals to change personal choice and behaviour.[5,175,176] A whole-system approach, involving many sectors, is crucial to tackling the obesity and salt epidemics.[5–7,175–180] Integrated action is required by national and local governments, industry and communities, and families and the societies in which they live. Potential policies include the following initiatives: to assess and understand the size and nature of the problem; to establish communication strategies to improve public knowledge about food and behaviours relating to food; to engage with the food industry to set fair and progressive standards and targets for nutrient contents in processed foods, food labelling, and market advertising; to implement multiple progressive interventions to change behaviours at all levels (individual, local, national, and global); and to serially monitor the effects of the above interventions.[176–180]

Population-wide salt-reduction programmes that are led by governments and engage with industry to remove salt at its source could be highly cost effective. In the USA, modest, population-wide reductions in dietary salt of up to 3 g per day (1·2 g of sodium per day) are projected to reduce the annual number of new cases of stroke by 32 000 to 66 000, similar to the benefits of population-wide reductions in tobacco use, obesity, and cholesterol levels.[181–183] The UK Government has accepted the challenge to set and enforce salt targets for foods.[63,176] The potential effect of adopting a healthy diet policy on population health, agricultural production, trade, the global economy, and livelihoods is likely to be substantial in some countries,[184] and the effects could be realised sooner than we think.[185]

Conflicts of interest

I was the principal investigator of the VITAmins TO Prevent Stroke (VITATOPS) trial. I have received honoraria for serving on the executive committees of the AMADEUS trial (Sanofi-Aventis), ROCKET-AF trial (Johnson & Johnson), and BOREALIS trial (Sanofi-Aventis), the steering committee of the TRA 2°P–TIMI 50 trial, the stroke outcome adjudication committee of the ACTIVE-W, ACTIVE-A, RE-LY, and AVERROES trials, and for speaking at sponsored scientific symposia and consulting on advisory boards for Bristol-Myers Squibb, Boehringer Ingelheim, Bayer, and Pfizer Australia.

References

1 Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009; **8:** 355–69.

2 Lloyd-Jones DM, Hong Y, Labarthe D, et al, and the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation* 2010; **121:** 586–613.

3 Lock K, Smith RD, Dangour AD, et al. Health, agricultural, and economic effects of adoption of healthy diet recommendations. *Lancet* 2010; **376:** 1699–709.

4 Dans A, Ng N, Varghese C, Tai ES, Firestone R, Bonita R. The rise of chronic non-communicable diseases in southeast Asia: time for action. *Lancet* 2011; **377:** 680–89.

5 Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet* 2011; **378:** 804–14.

6 Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet* 2011; **378:** 815–25.

7 Finucane MM, Stevens GA, Cowan MJ, et al, and the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. *Lancet* 2011; **377:** 557–67.

8 Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. *Lancet Neurol* 2007; **6:** 182–87.

9 Cecchini M, Sassi F, Lauer JA, Lee YY, Guajardo-Barron V, Chisholm D. Tackling of unhealthy diets, physical inactivity, and obesity: health effects and cost-effectiveness. *Lancet* 2010; **376:** 1775–84.

10 Franklin BA, Cushman M. Recent advances in preventive cardiology and lifestyle medicine: a themed series. *Circulation* 2011; **123:** 2274–83.

11 Sacco RL. Achieving ideal cardiovascular and brain health: opportunity amid crisis: Presidential Address at the American Heart Association 2010 Scientific Sessions. *Circulation* 2011; **123:** 2653–57.

12 Goldstein LB, Bushnell CD, Adams RJ, et al, and the American Heart Association Stroke Council, and the Council on Cardiovascular Nursing, and the Council on Epidemiology and Prevention, and the Council for High Blood Pressure Research, and the Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011; **42:** 517–84.

13 Saunders J, Smith T. Malnutrition: causes and consequences. *Clin Med* 2010; **10:** 624–27.

14 Foley NC, Salter KL, Robertson J, Teasell RW, Woodbury MG. Which reported estimate of the prevalence of malnutrition after stroke is valid? *Stroke* 2009; **40:** e66–74.

15 Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. *Am J Clin Nutr* 1998; **68:** 899–917.

16 Deurenberg P, Yap M, van Staveren WA. Body mass index and percent body fat: a meta analysis among different ethnic groups. *Int J Obes Relat Metab Disord* 1998; **22:** 1164–1171.

17 Bodenant M, Kuulasmaa K, Wagner A, et al, and the MORGAM Project. Measures of abdominal adiposity and the risk of stroke: the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) study. *Stroke* 2011; **42:** 2872–77.

18 Gariballa SE, Parker SG, Taub N, Castleden M. Nutritional status of hospitalized acute stroke patients. *Br J Nutr* 1998; **79:** 481–87.

19 Seliger SL, Gillen DL, Tirschwell D, Wasse H, Kestenbaum BR, Stehman-Breen CO. Risk factors for incident stroke among patients with end-stage renal disease. *J Am Soc Nephrol* 2003; **14:** 2623–31.

20 Gao C, Zhang B, Zhang W, Pu S, Yin J, Gao Q. Serum prealbumin (transthyretin) predict good outcome in young patients with cerebral infarction. *Clin Exp Med* 2011; **11:** 49–54.

21 Elia M, Stratton RJ. How much undernutrition is there in hospitals? *Br J Nutr* 2000; **84:** 257–59.

22 Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* 2006; **295:** 1549–55.

23 Ogden CL, Carroll MD, Flegal KM. High body mass index for age among US children and adolescents, 2003–2006. *JAMA* 2008; **299:** 2401–05.

24 Wang Y, Beydoun MA. The obesity epidemic in the United States—gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. *Epidemiol Rev* 2007; **29:** 6–28.

25 Atkins D, Best D, Briss PA, et al, and the GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; **328:** 1490.

26 Guyatt GH, Oxman AD, Vist GE, et al, and the GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336:** 924–26.

27 Lawlor DA, Davey Smith G, Kundu D, Bruckdorfer KR, Ebrahim S. Those confounded vitamins: what can we learn from the differences between observational versus randomised trial evidence? *Lancet* 2004; **363:** 1724–27.

28 Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965; **58:** 295–300.

29 Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med* 2009; **169:** 659–69.

30 Martyn CN, Barker DJP, Osmond C. Mothers' pelvic size, fetal growth, and death from stroke and coronary heart disease in men in the UK. *Lancet* 1996; **348:** 1264–68.

31 Osmond C, Kajantie E, Forsén TJ, Eriksson JG, Barker DJP. Infant growth and stroke in adult life: the Helsinki birth cohort study. *Stroke* 2007; **38:** 264–70.

32 Eriksson JG, Forsén T, Tuomilehto J, Osmond C, Barker DJ. Early growth, adult income, and risk of stroke. *Stroke* 2000; **31:** 869–74.

33 Barker DJP, Lackland DT. Prenatal influences on stroke mortality in England and Wales. *Stroke* 2003; **34:** 1598–602.

34 Glymour MM, Avendaño M, Berkman LF. Is the 'stroke belt' worn from childhood?: risk of first stroke and state of residence in childhood and adulthood. *Stroke* 2007; **38:** 2415–21.

35 Whitlock G, Lewington S, Sherliker P, et al, and the Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009; **373:** 1083–96.

36 Yatsuya H, Folsom AR, Yamagishi K, North KE, Brancati FL, Stevens J, and the Atherosclerosis Risk in Communities Study Investigators. Race- and sex-specific associations of obesity measures with ischemic stroke incidence in the Atherosclerosis Risk in Communities (ARIC) study. *Stroke* 2010; **41:** 417–25.

37 Kurth T, Gaziano JM, Berger K, et al. Body mass index and the risk of stroke in men. *Arch Intern Med* 2002; **162:** 2557–62.

38 Kurth T, Gaziano JM, Rexrode KM, et al. Prospective study of body mass index and risk of stroke in apparently healthy women. *Circulation* 2005; **111:** 1992–98.

39 Song Y-M, Sung J, Davey Smith G, Ebrahim S. Body mass index and ischemic and hemorrhagic stroke: a prospective study in Korean men. *Stroke* 2004; **35:** 831–36.

40 Ni Mhurchu C, Rodgers A, Pan WH, Gu DF, Woodward M, and the Asia Pacific Cohort Studies Collaboration. Body mass index and cardiovascular disease in the Asia-Pacific Region: an overview of 33 cohorts involving 310 000 participants. *Int J Epidemiol* 2004; **33:** 751–58.

41 Winter Y, Rohrmann S, Linseisen J, et al. Contribution of obesity and abdominal fat mass to risk of stroke and transient ischemic attacks. *Stroke* 2008; **39:** 3145–51.

42 Furukawa Y, Kokubo Y, Okamura T, et al. The relationship between waist circumference and the risk of stroke and myocardial infarction in a Japanese urban cohort: the Suita study. *Stroke* 2010; **41:** 550–53.

43 Saito I, Iso H, Kokubo Y, Inoue M, Tsugane S. Body mass index, weight change and risk of stroke and stroke subtypes: the Japan Public Health Center-based prospective (JPHC) study. *Int J Obes (Lond)* 2011; **35:** 283–91.

44 Kizer JR, Biggs ML, Ix JH, et al. Measures of adiposity and future risk of ischemic stroke and coronary heart disease in older men and women. *Am J Epidemiol* 2011; **173:** 10–25.

45 O'Donnell MJ, Xavier D, Liu L, et al, and the INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010; **376:** 112–23.

46 Wormser D, Kaptoge S, Di Angelantonio E, et al, and the Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet* 2011; **377:** 1085–95.

47 Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA* 2007; **297:** 842–57.

48 Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet* 2003; **361:** 2017–23.

49 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360:** 23–33.

50 Cook NR, Albert CM, Gaziano JM, et al. A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women's Antioxidant Cardiovascular Study. *Arch Intern Med* 2007; **167:** 1610–18.

51 Sesso HD, Buring JE, Christen WG, et al. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA* 2008; **300:** 2123–33.

52 Bin Q, Hu X, Cao Y, Gao F. The role of vitamin E (tocopherol) supplementation in the prevention of stroke. A meta-analysis of 13 randomised controlled trials. *Thromb Haemost* 2011; **105:** 579–85.

53 Clarke R, Halsey J, Lewington S, et al, and the B-Vitamin Treatment Trialists' Collaboration. Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: meta-analysis of 8 randomized trials involving 37 485 individuals. *Arch Intern Med* 2010; **170:** 1622–31.

54 Holmes MV, Newcombe P, Hubacek JA, et al. Effect modification by population dietary folate on the association between *MTHFR* genotype, homocysteine, and stroke risk: a meta-analysis of genetic studies and randomised trials. *Lancet* 2011; **378:** 584–94.

55 Pittas AG, Chung M, Trikalinos T, et al. Systematic review: vitamin D and cardiometabolic outcomes. *Ann Intern Med* 2010; **152:** 307–14.

56 Wang L, Manson JE, Song Y, Sesso HD. Systematic review: vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med* 2010; **152:** 315–23.

57 Manson JE. Vitamin D and the heart: why we need large-scale clinical trials. *Cleve Clin J Med* 2010; **77:** 903–10.

58 Strazzullo P, D'Elia L, Kandala N-B, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ* 2009; **339:** b4567.

59 He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. *Lancet* 2011; **378:** 380–82.

60 Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease: a meta-analysis of randomized controlled trials (Cochrane review). *Am J Hypertens* 2011; **24:** 843–53.

61 Pimenta E, Gaddam KK, Oparil S, et al. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. *Hypertension* 2009; **54:** 475–81.

62 Sacks FM, Campos H. Dietary therapy in hypertension. *N Engl J Med* 2010; **362:** 2102–12.

63 Webster JL, Dunford EK, Hawkes C, Neal BC. Salt reduction initiatives around the world. *J Hypertens* 2011; **29:** 1043–50.

64 MacGregor GA, Markandu ND, Sagnella GA, Singer DR, Cappuccio FP. Double-blind study of three sodium intakes and long-term effects of sodium restriction in essential hypertension. *Lancet* 1989; **2:** 1244–47.

65 Vollmer WM, Sacks FM, Ard J, et al, and the DASH-Sodium Trial Collaborative Research Group. Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. *Ann Intern Med* 2001; **135:** 1019–28.

66 Larsson SC, Orsini N, Wolk A. Dietary potassium intake and risk of stroke: a dose-response meta-analysis of prospective studies. *Stroke* 2011; **42:** 2746–50.

67 Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA* 1997; **277:** 1624–32.

68 Dickinson HO, Nicolson DJ, Campbell F, Beyer FR, Mason J. Potassium supplementation for the management of primary hypertension in adults. *Cochrane Database Syst Rev* 2006; **3:** CD004641.

69 Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010; **341:** c3691.

70 Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ* 2011; **342:** d2040.

71 He K, Merchant A, Rimm EB, et al. Dietary fat intake and risk of stroke in male US healthcare professionals: 14 year prospective cohort study. *BMJ* 2003; **327:** 777–82.

72 Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 2006; **295:** 655–66.

73 Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr* 2010; **91:** 535–46.

74 Marik PE, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. *Clin Cardiol* 2009; **32:** 365–72.

75 Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S, and the SU.FOL.OM3 Collaborative Group. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. *BMJ* 2010; **341:** c6273.

76 de Goede J, Verschuren WMM, Boer JMA, Kromhout D, Geleijnse JM. Alpha-linolenic acid intake and 10-year incidence of coronary heart disease and stroke in 20,000 middle-aged men and women in the Netherlands. *PLoS One* 2011; **6:** e17967. DOI:10.1371/journal.pone.0017967.

77 Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health: a systematic review and meta-analysis: relations between dietary glycemic properties and health outcomes. *Am J Clin Nutr* 2008; **87:** 258S–68S.

78 Oba S, Nagata C, Nakamura K, et al. Dietary glycemic index, glycemic load, and intake of carbohydrate and rice in relation to risk of mortality from stroke and its subtypes in Japanese men and women. *Metabolism* 2010; **59:** 1574–82.

79 Whelton SP, Hyre AD, Pedersen B, Yi Y, Whelton PK, He J. Effect of dietary fiber intake on blood pressure: a meta-analysis of randomized, controlled clinical trials. *J Hypertens* 2005; **23:** 475–81.

80 Preis SR, Stampfer MJ, Spiegelman D, Willett WC, Rimm EB. Lack of association between dietary protein intake and risk of stroke among middle-aged men. *Am J Clin Nutr* 2010; **91:** 39–45.

81 Navab M, Ananthramaiah GM, Reddy ST, et al. The oxidation hypothesis of atherogenesis: the role of oxidized phospholipids and HDL. *J Lipid Res* 2004; **45:** 993–1007.

82 Myint PK, Luben RN, Welch AA, Bingham SA, Wareham NJ, Khaw K-T. Plasma vitamin C concentrations predict risk of incident stroke over 10 y in 20 649 participants of the European Prospective Investigation into Cancer Norfolk prospective population study. *Am J Clin Nutr* 2008; **87:** 64–69.

83 Kubota Y, Iso H, Date C, et al. the JACC study group. Dietary intakes of antioxidant vitamins and mortality from cardiovascular disease: the Japan Collaborative Cohort Study (JACC) study. *Stroke* 2011; **42:** 1665–72.

84 Clarke MW, Burnett JR, Croft KD. Vitamin E in human health and disease. *Crit Rev Clin Lab Sci* 2008; **45:** 417–50.

85 Schürks M, Glynn RJ, Rist PM, Tzourio C, Kurth T. Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials. *BMJ* 2010; **341:** c5702.

86 Wald DS, Wald NJ, Morris JK, Law M. Folic acid, homocysteine, and cardiovascular disease: judging causality in the face of inconclusive trial evidence. *BMJ* 2006; **333:** 1114–17.

87 Hassan A, Hunt BJ, O'Sullivan M, et al. Homocysteine is a risk factor for cerebral small vessel disease, acting via endothelial dysfunction. *Brain* 2004; **127:** 212–19.

88 Eikelboom JW, Hankey GJ, Anand SS, Lofthouse E, Staples N, Baker RI. Association between high homocyst(e)ine and ischemic stroke due to large- and small-artery disease but not other etiologic subtypes of ischemic stroke. *Stroke* 2000; **31:** 1069–75.

89 Poli D, Antonucci E, Cecchi E, et al. Culprit factors for the failure of well-conducted warfarin therapy to prevent ischemic events in patients with atrial fibrillation: the role of homocysteine. *Stroke* 2005; **36:** 2159–63.

90 Homocysteine Lowering Trialists' Collaboration. Dose-dependent effects of folic acid on blood concentrations of homocysteine: a meta-analysis of the randomized trials. *Am J Clin Nutr* 2005; **82:** 806–12.

91 Flicker L, Vasikaran SD, Thomas J, et al. Efficacy of B vitamins in lowering homocysteine in older men: maximal effects for those with B12 deficiency and hyperhomocysteinemia. *Stroke* 2006; **37:** 547–49.

92 Spence JD, Bang H, Chambless LE, Stampfer MJ. Vitamin Intervention For Stroke Prevention trial: an efficacy analysis. *Stroke* 2005; **36:** 2404–09.

93 Lonn E, Yusuf S, Arnold MJ, et al, and the Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006; **354:** 1567–77.

94 Deshmukh US, Joglekar CV, Lubree HG, et al. Effect of physiological doses of oral vitamin B12 on plasma homocysteine: a randomized, placebo-controlled, double-blind trial in India. *Eur J Clin Nutr* 2010; **64:** 495–502.

95 Carrelli AL, Walker MD, Lowe H, et al. Vitamin D deficiency is associated with subclinical carotid atherosclerosis: the Northern Manhattan study. *Stroke* 2011; **42:** 2240–45.

96 Witham MD, Dove FJ, Sugden JA, Doney AS, Struthers AD. The effect of vitamin D replacement on markers of vascular health in stroke patients—a randomised controlled trial. *Nutr Metab Cardiovasc Dis* 2010; published online Dec 29. DOI:10.1016/j.numecd.2010.11.001.

97 Mursu J, Robien K, Harnack LJ, Park K, Jacobs DR Jr. Dietary supplements and mortality rate in older women: the Iowa Women's Health Study. *Arch Intern Med* 2011; **171:** 1625–33.

98 Jamrozik K, Broadhurst RJ, Anderson CS, Stewart-Wynne EG. The role of lifestyle factors in the etiology of stroke. A population-based case-control study in Perth, Western Australia. *Stroke* 1994; **25:** 51–59.

99 Frohlich ED. The salt conundrum: a hypothesis. *Hypertension* 2007; **50:** 161–66.

100 He FJ, MacGregor GA. Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. *J Hum Hypertens* 2002; **16:** 761–70.

101 He FJ, MacGregor GA. Importance of salt in determining blood pressure in children: meta-analysis of controlled trials. *Hypertension* 2006; **48:** 861–69.

102 D'Elia L, Barba G, Cappuccio FP, Strazzullo P. Potassium intake, stroke, and cardiovascular disease a meta-analysis of prospective studies. *J Am Coll Cardiol* 2011; **57:** 1210–19.

103 Sambrook P, Cooper C. Osteoporosis. *Lancet* 2006; **367:** 2010–18.

104 Tang BMP, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* 2007; **370:** 657–66.

105 Griffith LE, Guyatt GH, Cook RJ, Bucher HC, Cook DJ. The influence of dietary and nondietary calcium supplementation on blood pressure: an updated metaanalysis of randomized controlled trials. *Am J Hypertens* 1999; **12:** 84–92.

106 Reid IR, Horne A, Mason B, Ames R, Bava U, Gamble GD. Effects of calcium supplementation on body weight and blood pressure in normal older women: a randomized controlled trial. *J Clin Endocrinol Metab* 2005; **90:** 3824–29.

107 Reid IR, Mason B, Horne A, et al. Effects of calcium supplementation on serum lipid concentrations in normal older women: a randomized controlled trial. *Am J Med* 2002; **112:** 343–47.

108 Iso H, Stampfer MJ, Manson JE, et al. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. *Stroke* 1999; **30:** 1772–79.

109 Umesawa M, Iso H, Ishihara J, et al, and the JPHC Study Group. Dietary calcium intake and risks of stroke, its subtypes, and coronary heart disease in Japanese: the JPHC Study Cohort I. *Stroke* 2008; **39:** 2449–56.

110 Larsson SC, Virtamo J, Wolk A. Potassium, calcium, and magnesium intakes and risk of stroke in women. *Am J Epidemiol* 2011; **174:** 35–43.

111 Abrahamsen B, Sahota O. Do calcium plus vitamin D supplements increase cardiovascular risk? *BMJ* 2011; **342:** d2080.

112 Christensen S, Mehnert F, Chapurlat RD, Baron JA, Sørensen HT. Oral bisphosphonates and risk of ischemic stroke: a case-control study. *Osteoporos Int* 2011; **22:** 1773–79.

113 Mozaffarian D, Appel LJ, Van Horn L. Components of a cardioprotective diet: new insights. *Circulation* 2011; **123:** 2870–91.

114 Jakobsen MU, O'Reilly EJ, Heitmann BL, et al. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. *Am J Clin Nutr* 2009; **89:** 1425–32.

115 Mozaffarian D, Aro A, Willett WC. Health effects of trans-fatty acids: experimental and observational evidence. *Eur J Clin Nutr* 2009; **63** (suppl 2)**:** S5–21.

116 Mozaffarian D, Stampfer MJ. Removing industrial trans fat from foods. *BMJ* 2010; **340:** c1826.

117 Micha R, Mozaffarian D. Saturated fat and cardiometabolic risk factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence. *Lipids* 2010; **45:** 893–905.

118 Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med* 2010; **7:** e1000252.

119 Saravanan P, Davidson NC, Schmidt EB, Calder PC. Cardiovascular effects of marine omega-3 fatty acids. *Lancet* 2010; **376:** 540–50.

120 Johnson RK, Appel LJ, Brands M, et al, and the American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism and the Council on Epidemiology and Prevention. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. *Circulation* 2009; **120:** 1011–20.

121 Sieri S, Krogh V, Berrino F, et al. Dietary glycemic load and index and risk of coronary heart disease in a large italian cohort: the EPICOR study. *Arch Intern Med* 2010; **170:** 640–47.

122 Jakobsen MU, Dethlefsen C, Joensen AM, et al. Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycemic index. *Am J Clin Nutr* 2010; **91:** 1764–68.

123 Sauvaget C, Nagano J, Hayashi M, Yamada M. Animal protein, animal fat, and cholesterol intakes and risk of cerebral infarction mortality in the adult health study. *Stroke* 2004; **35:** 1531–37.

124 Larsson SC, Orsini N. Fish consumption and risk of stroke. A dose-response meta-analysis. *Stroke* 2011; published online Sept 8. DOI:10.1161/STROKEAHA.111.630319.

125 He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet* 2006; **367:** 320–26.

126 John JH, Ziebland S, Yudkin P, Roe LS, Neil HAW, and the Oxford Fruit and Vegetable Study Group. Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial. *Lancet* 2002; **359:** 1969–74.

127 Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. *Circulation* 2010; **121:** 2271–83.

128 Larsson SC, Virtamo J, Wolk A. Red meat consumption and risk of stroke in Swedish men. *Am J Clin Nutr* 2011; **94:** 417–21.

129 Soedamah-Muthu SS, Ding EL, Al-Delaimy WK, et al. Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. *Am J Clin Nutr* 2011; **93:** 158–71.

130 Buitrago-Lopez A, Sanderson J, Johnson L, et al. Chocolate consumption and cardiometabolic disorders: systematic review and meta-analysis. *BMJ* 2011; **343:** d4488.

131 Larsson SC, Orsini N. Coffee consumption and risk of stroke: a dose-response meta-analysis of prospective studies. *Am J Epidemiol* 2011; **174:** 993–1001.

132 Larsson SC, Virtamo J, Wolk A. Coffee consumption and risk of stroke in women. *Stroke* 2011; **42:** 908–12.

133 Arab L, Liu W, Elashoff D. Green and black tea consumption and risk of stroke: a meta-analysis. *Stroke* 2009; **40:** 1786–92.

134 Chen L, Appel LJ, Loria C, et al. Reduction in consumption of sugar-sweetened beverages is associated with weight loss: the PREMIER trial. *Am J Clin Nutr* 2009; **89:** 1299–306.

135 Malik VS, Popkin BM, Bray GA, Després JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes Care* 2010; **33:** 2477–83.

136 Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. *Am J Clin Nutr* 2009; **89:** 1037–42.

137 Mellen PB, Walsh TF, Herrington DM. Whole grain intake and cardiovascular disease: a meta-analysis. *Nutr Metab Cardiovasc Dis* 2008; **18:** 283–90.

138 Eshak ES, Iso H, Date C, et al, and the JACC Study Group. Rice intake is associated with reduced risk of mortality from cardiovascular disease in Japanese men but not women. *J Nutr* 2011; **141:** 595–602.

139 Myint PK, Welch AA, Bingham SA, et al. Habitual fish consumption and risk of incident stroke: the European Prospective Investigation into Cancer (EPIC)-Norfolk prospective population study. *Public Health Nutr* 2006; **9:** 882–88.

140 Atkinson C, Whitley E, Ness A, Baker I. Associations between types of dietary fat and fish intake and risk of stroke in the Caerphilly Prospective Study (CaPS). *Public Health* 2011; **125:** 345–48.

141 Larsson SC, Virtamo J, Wolk A. Fish consumption and risk of stroke in Swedish women. *Am J Clin Nutr* 2011; **93:** 487–93.

142 Iso H, Rexrode KM, Stampfer MJ, et al. Intake of fish and omega-3 fatty acids and risk of stroke in women. *JAMA* 2001; **285:** 304–12.

143 Bouzan C, Cohen JT, Connor WE, et al. A quantitative analysis of fish consumption and stroke risk. *Am J Prev Med* 2005; **29:** 347–52.

144 Wang C, Harris WS, Chung M, et al. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr* 2006; **84:** 5–17.

145 Mozaffarian D, Wu JHY. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J Am Coll Cardiol* 2011; **58:** 2047–67.

146 Goldbohm RA, Chorus AM, Galindo Garre F, Schouten LJ, van den Brandt PA. Dairy consumption and 10-y total and cardiovascular mortality: a prospective cohort study in the Netherlands. *Am J Clin Nutr* 2011; **93:** 615–27.

147 Mesas AE, Leon-Muñoz LM, Rodriguez-Artalejo F, Lopez-Garcia E. The effect of coffee on blood pressure and cardiovascular disease in hypertensive individuals: a systematic review and meta-analysis. *Am J Clin Nutr* 2011; **94:** 1113–26.

148 Mostofsky E, Schlaug G, Mukamal KJ, Rosamond WD, Mittleman MA. Coffee and acute ischemic stroke onset: the Stroke Onset Study. *Neurology* 2010; **75:** 1583–88.

149 Hooper L, Kroon PA, Rimm EB, et al. Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2008; **88:** 38–50.

150 Jochmann N, Lorenz M, Krosigk A, et al. The efficacy of black tea in ameliorating endothelial function is equivalent to that of green tea. *Br J Nutr* 2008; **99:** 863–68.

151 Tinahones FJ, Rubio MA, Garrido-Sánchez L, et al. Green tea reduces LDL oxidability and improves vascular function. *J Am Coll Nutr* 2008; **27:** 209–13.

152 Hooper L, Kroon PA, Rimm EB, et al. Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2008; **88:** 38–50.

153 Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M, and the American Heart Association Nutrition Committee. Soy protein, isoflavones, and cardiovascular health: an American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation* 2006; **113:** 1034–44.

154 Kurth T, Moore SC, Gaziano JM, et al. Healthy lifestyle and the risk of stroke in women. *Arch Intern Med* 2006; **166:** 1403–09.

155 Chiuve SE, Rexrode KM, Spiegelman D, Logroscino G, Manson JE, Rimm EB. Primary prevention of stroke by healthy lifestyle. *Circulation* 2008; **118:** 947–54.

156 Fung TT, Stampfer MJ, Manson JE, Rexrode KM, Willett WC, Hu FB. Prospective study of major dietary patterns and stroke risk in women. *Stroke* 2004; **35:** 2014–19.

157 Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. *Arch Intern Med* 2008; **168:** 713–20.

158 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:** 1093–100.

159 Yau WY, Hankey GJ. Which dietary and lifestyle behaviours may be important in the aetiology (and prevention) of stroke? *J Clin Neurosci* 2011; **18:** 76–80.

160 Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr* 2010; **92:** 1189–96.

161 Appel LJ, Moore TJ, Obarzanek E, et al, and the DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997; **336:** 1117–24.

162 Estruch R, Martinez-Gonzalez MA, Corella D, et al, for the PREDIMED Study Investigators. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med* 2006; **145:** 1–11.

163 Fitó M, Guxens M, Corella D, et al, and the for the PREDIMED Study Investigators. Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial. *Arch Intern Med* 2007; **167:** 1195–203.

164 Shai I, Schwarzfuchs D, Henkin Y, et al, and the Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008; **359:** 229–41.

165 Sciarrone SE, Strahan MT, Beilin LJ, Burke V, Rogers P, Rouse IR. Ambulatory blood pressure and heart rate responses to vegetarian meals. *J Hypertens* 1993; **11:** 277–85.

166 Burke LE, Hudson AG, Warziski MT, et al. Effects of a vegetarian diet and treatment preference on biochemical and dietary variables in overweight and obese adults: a randomized clinical trial. *Am J Clin Nutr* 2007; **86:** 588–96.

167 Key TJ, Fraser GE, Thorogood M, et al. Mortality in vegetarians and non-vegetarians: a collaborative analysis of 8300 deaths among 76,000 men and women in five prospective studies. *Public Health Nutr* 1998; **1:** 33–41.

168 Willcox BJ, Willcox DC, Todoriki H, et al. Caloric restriction, the traditional Okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span. *Ann N Y Acad Sci* 2007; **1114:** 434–55.

169 Willcox DC, Willcox BJ, Todoriki H, Suzuki M. The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. *J Am Coll Nutr* 2009; **28** (suppl)**:** 500S–16S.

170 Oba S, Nagata C, Nakamura K, et al. Dietary glycemic index, glycemic load, and intake of carbohydrate and rice in relation to risk of mortality from stroke and its subtypes in Japanese men and women. *Metabolism* 2010; **59:** 1574–82.

171 Tada N, Maruyama C, Koba S, et al. Japanese dietary lifestyle and cardiovascular disease. *J Atheroscler Thromb* 2011; **18:** 723–34.

172 Shimazu T, Kuriyama S, Hozawa A, et al. Dietary patterns and cardiovascular disease mortality in Japan: a prospective cohort study. *Int J Epidemiol* 2007; **36:** 600–09.

173 Iso H. Lifestyle and cardiovascular disease in Japan. *J Atheroscler Thromb* 2011; **18:** 83–88.

174 Hawkes N. Take dietary truths with a pinch of salt. *BMJ* 2011; **343:** d5346.

175 King D. The future challenge of obesity. *Lancet* 2011; **378:** 743–44.

176 Cappuccio FP, Capewell S, Lincoln P, McPherson K. Policy options to reduce population salt intake. *BMJ* 2011; **343:** d4995.

177 Campbell NRC, Legowski B, Legetic B. Mobilising the Americas for dietary salt reduction. *Lancet* 2011; **377:** 793–95.

178 Kopelman P. Symposium 1: Overnutrition: consequences and solutions. Foresight Report: the obesity challenge ahead. *Proc Nutr Soc* 2010; **69:** 80–85.

179 Gortmaker SL, Swinburn BA, Levy D, et al. Changing the future of obesity: science, policy, and action. *Lancet* 2011; **378:** 838–47.

180 Mozaffarian D, Capewell SU. United Nations' dietary policies to prevent cardiovascular disease. *BMJ* 2011; **343:** d5747.

181 He FJ, MacGregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *J Hum Hypertens* 2009; **23:** 363–84.

182 Bibbins-Domingo K, Chertow GM, Coxson PG, et al. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med* 2010; **362:** 590–99.

183 Appel LJ, Frohlich ED, Hall JE, et al. The importance of population-wide sodium reduction as a means to prevent cardiovascular disease and stroke: a call to action from the American Heart Association. *Circulation* 2011; **123:** 1138–43.

184 Lock K, Smith RD, Dangour AD, et al. Health, agricultural, and economic effects of adoption of healthy diet recommendations. *Lancet* 2010; **376:** 1699–709.

185 Capewell S, O'Flaherty M. Rapid mortality falls after risk-factor changes in populations. *Lancet* 2011; **378:** 752–53.