# Review article

# Nutritional factors in stroke

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Observational studies support the role of modifying lifestyle-related risk factors such as diet, physical activity and alcohol use in stroke prevention. For example, increased Na intake is associated with hypertension, and reduction in salt consumption may significantly lower blood pressure and may reduce stroke mortality. Moderately elevated homocysteine levels may be associated with stroke and are associated with deficiency of dietary intake of folate, vitamin $B_6$ and vitamin $B_{12}$. Consumption of a diet rich in fruits, vegetables, folate, K, Ca, Mg, dietary fibre, fish and milk may protect against stroke. Regular physical activity may also protect against stroke through its role in controlling various risk factors such as hypertension, diabetes mellitus and obesity. The role of fat intake as a risk factor for stroke remains uncertain, whereas the association between stroke and cholesterol has more convincingly been demonstrated by the recent intervention trials using statins. There is also evidence that a low serum albumin may be causally linked to stroke risk and outcome and that a significant number of stroke patients are undernourished on admission and their nutritional status deteriorates further whilst in hospital. Undernutrition is associated with increasing morbidity and mortality and nutritional supplements may have some beneficial effect on some outcome measures.

**Stroke: Stroke prevention**

Stroke is the third most common cause of death in most western populations after IHD and cancer (Warlow *et al*. 1996*a*). It is thus the commonest life-threatening neurological disorder, and the resulting disability is the most important single cause of severe disability among western people living in their own homes (Martin *et al*. 1988). Approximately 100 000 and 500 000 new or recurrent strokes occur each year in the UK and the USA respectively. Stroke in the developing world is less well documented. A consensus statement from the Asia-Pacific Consensus Forum on Stroke Management predicts that: 'In the next 30 years the burden of stroke will grow most in developing countries rather than in developed world' (Poungvarin, 1998). The majority of strokes (about 80 %) are due to cerebral infarction, 10 % are due to primary intracerebral haemorrhage, 5 % to subarachnoid haemorrhage and in 5 % the cause is uncertain (Warlow *et al*. 1996*b*). This classification of stroke subtypes is only possible if a computed tomographic scan of the brain is available.

A steady fall in mortality rates from cerebrovascular disease has been observed over at least three decades in Britain, and the USA for much longer. Although improvement in the rate of detection and treatment of established risk factors such as hypertension is part of the reason for the fall, no satisfactory explanation has so far been given (Vartiainen *et al*. 1995). Data from epidemiological studies suggest that immigrants rapidly take on the stroke incidence rates of their adopted country (Syme *et al*. 1975). Thus environmental factors, including diet, may be important in the genesis of stroke and in the potential to prevent its occurrence. Well documented changes in eating habits, among them an increase in intake of fruits and vegetables and a fall in salt intake are known to have taken place over this period (Acheson & Williams, 1983). It is also possible that dietary problems not only influence the prevalence of stroke but its course and outcome once it has occurred. The object of this present review is to discuss published work on these subjects to see if there is evidence to alter the current public health messages on prevention and management of stroke. The published literature was obtained using a key word and key author search of MEDLINE and the Science Citation Index (English

**Abbreviation:** PEG, percutaneous endoscopic gastrostomy.

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language; hppt://biomed.niss.ac.uk) focused on the period 1961–98, and supplemented by following up the references in any article drawn from this search. This research yield over 400 articles for consideration but closer inspection showed that fewer than 25 % of these articles shed any light on the subject.

## Role of nutritional factors in stroke incidence and outcome

### *Fruits and vegetables (antioxidants)*

There are several reasons why an increased consumption of fruits and vegetables is desirable in the national diet. They are a rich source of NSP and vitamins and minerals. Several of these micronutrients have antioxidant properties and they may have a role in protecting against free radical-induced oxidative stress which has been linked with the pathogenesis of IHD and ischaemic stroke and other diseases (Gey *et al*. 1993*a*). These essential antioxidants include vitamins C, E and A and carotenoids, and their concentrations in the body fluids is determined mainly by dietary intake (Gey *et al*. 1993*a*). Table 1 shows some of the recent epidemiological studies investigating the association between antioxidants and incidence of ischaemic stroke. In Britain for example, rates of strokes and IHD are highest in regions where consumption of fruits and vegetables is lowest (Acheson & Williams, 1983). This epidemiological study suggested an inverse association between fruits and vegetables consumption and incidence of stroke (Acheson & Williams, 1983). However the results of this study should be interpreted with caution as the gross population comparisons set out were based on comparisons between retrospective mortality statistics, environmental temperature and geographical pattern for disease distribution.

Many epidemiological studies from all over the world have led to the assumption that vegetable-rich diets are associated with a higher life expectancy, and antioxidants could be of principal importance for the benefits of vegetable-rich diets. There are three major complementary epidemiological studies of the relationship between the plasma concentration of diet-derived antioxidants and the risk of IHD and stroke: (1) the WHO/MONICA project (World Health Organization, 1989), which was a cross-cultural comparison of randomly selected representatives of sixteen European study populations; (2) the Edinburgh Angina-Control study (Riemersma *et al*. 1991), which was a case–control study of 110 undiagnosed and untreated angina pectoris sufferers and 394 matched controls identified by postal questionnaires from 600 males; (3) the Basel Prospective study (Gey *et al*. 1993*b*) of 2974 men from the working population, 50 (SD 9) years of age. These studies consistently revealed an increased risk of IHD (and stroke) at low plasma concentrations of antioxidants. During a 12-year follow-up in the Basel Prospective study, 132 subjects died of IHD and thirty-one of stroke. Subjects with low concentrations of both carotene and vitamin C had a significantly higher risk of death from these conditions. Manson *et al*. (1993) assessed consumption of antioxidant vitamins using a semiquantitative food frequency questionnaire in 87 245 female nurses in the USA aged 34–59. Subjects who were free of diagnosed IHD and cancer were followed-up for 8 years. It was found that higher antioxidant vitamin consumption was associated with a reduced risk of ischaemic stroke in women. Two large cohort follow-up studies were reported 1995; first, from the UK (Gale *et al*. 1995), a 20-year follow-up of 730 randomly selected elderly people free of history or symptoms of stroke or IHD living in the community. All the subjects had their vitamin C status assessed by dietary intake and plasma concentration. During 20 years follow-up, 643 subjects died. There were 124 deaths from stroke. Mortality from stroke was highest in those who had the lowest vitamin C levels, and low vitamin C status whether measured by plasma concentration or dietary intake, was strongly related to subsequent risk of death from stroke but not from IHD. The second study was part of the Framingham population-based longitudinal study (Gilman *et al*. 1995) in which the diets of 832 men, aged 45–65 years, were assessed by a single 24-h recall, and subjects were followed-up for 20 years. The risk of completed stroke or transient ischaemic attack was adjusted for BMI, cigarette smoking, glucose intolerance, physical activity, blood pressure, serum cholesterol, and energy, ethanol and fat intake. There was an inverse association between fruit and vegetable intake and the development of stroke however, and the authors concluded that the intake of fruits and vegetables may protect against development of stroke in men. Habitual intake of flavonoids and their major source (tea) may also protect against stroke (Keli *et al*. 1996).

In a small hospital-based study the vitamin C status was assessed by dietary intake and plasma vitamin C in a non-randomly selected group of patients with a high probability of cerebral thrombosis and in controls age-matched within 5 years. The study failed to demonstrate a relationship between vitamin C status and the risk of stroke (Barer *et al*. 1989).

Hitherto little was known about the possible protective effect of antioxidants and their concentrations during and immediately following acute ischaemic stroke and functional outcome. De Keyser *et al*. (1992) studied serum concentrations of vitamins A and E in eighty patients with acute middle cerebral artery ischaemia within 24 h of admission and compared them with eighty controls matched for age and sex who had various neurological disorders other than acute cerebral ischaemia. Outcome was assessed within the first 21 d. Their results suggested a beneficial effect of a high serum vitamin A concentration on early outcome in ischaemic stroke. However, a recent randomized trial in 22 071 male doctors aged 40–84 years found that $\beta$-carotene had no effect on incidences of cancer, cardiovascular disease and stroke after 14 years of follow-up (Hennekens *et al*. 1996).

### *Dietary and serum potassium*

Increased K intake which results from eating more fruits and vegetables is likely to be beneficial. Studies in hypertensive rats have found that a high K intake protects against death from stroke even though blood pressure was not affected (Tobian *et al*. 1985). Khaw & Barrett-Connor (1987) reported an inverse association of K intake, irrespective of

**Table 1.** Epidemiological trials investigating the association between fruits and vegetables (antioxidants) intake and incidence of stroke

| Authors and country | Subjects | Sample size (*n*) | Age of subjects (years) | Length of follow-up (years) | Antioxidants studied | Endpoints | Comments |
|---|---|---|---|---|---|---|---|
| Gey *et al.* (1993*b*), Switzerland | Men of the working population | 2974 | 50 (SD 9) | 12 | Plasma carotene and vitamin C | Thirty-one incident strokes | Increased incidence of stroke at low concentration of both vitamin C and plasma carotene (risk adjusted for age, smoking, blood pressure and cholesterol) |
| Manson *et al.* (1993), USA | Female nurses free of diagnosed IHD and cancer at baseline (1980) | 87 245 | 34–59 | 8 | Dietary carotene and vitamins C and E | 183 incident strokes | After adjustment for age, smoking and other cardiovascular risk factors, higher antioxidant vitamin consumption (all three) is associated with a reduced risk of ischaemic stroke |
| Gale *et al.* (1995), UK | Randomly selected elderly people (1973–4) free of history or symptoms of stroke or IHD living in the community | 730 | ≥65 | 20 | Dietary and plasma vitamin C | 643 died (124 because of stroke) | Mortality from stroke was highest in those who had the lowest vitamin C levels. Low vitamin C, whether measured by plasma concentration or dietary intake, was strongly related to subsequent risk of death from stroke but not from IHD |
| Gillman *et al.* (1995), USA | Framingham population-based longitudinal study. Men free of cardiovascular disease at baseline (1966–9) | 832 | 45–65 | >20 | Estimated servings per d of fruits and vegetables from a single 24 h diet recall at baseline | Ninety-seven incident strokes (seventy-three completed strokes and twenty-four transient ischaemic attacks) | The risk of completed stroke or transient ischaemic attack was adjusted for BMI, cigarette smoking, glucose intolerance, physical activity, blood pressure, serum cholesterol, and energy, ethanol and fat intake. There was an inverse association between fruit and vegetable intake and the development of stroke so that the intake of fruit and vegetables may protect against development of stroke in men |
| Keli *et al.* (1996), The Netherlands | Randomly selected men free of stroke from the town of Zutphen (1960) | 552 | 50–69 | 15 | Dietary history taken in 1960, 1965 and 1970 | Forty-two incident strokes | After adjusting for age, systolic blood pressure, serum cholesterol, smoking, energy intake and consumption of fish and alcohol, dietary flavonoids (quercetin) and $\beta$-carotene intake were inversely associated with stroke incidence. Intake of vitamins C and E was not associated with stroke risk |
| Khaw & Barrett-Connor (1987), USA | A sub-sample of 30 % of a defined upper-middle class white community in Rancho Bernardo, CA, USA who participated in a survey of risk factors for heart disease | 859 | 50–79 | 12 | 24 h dietary K intake at baseline | Twenty-four died of stroke | An inverse association of K intake, irrespective of hypertensive status, with stroke mortality so that high dietary intake of K may protect against stroke-associated death |

hypertensive status, with stroke mortality in a population-based cohort study in southern California, USA. A recent study found that hypokalaemia and lower 24 h urine excretion of K were more common in stroke patients than control groups and hypokalaemia post-stroke was associated with poor outcome (Gariballa *et al*. 1997). Clinical, experimental and epidemiological evidence suggests that a high dietary intake of K is associated with lower blood pressure which is the most important known risk factor for stroke (Langford, 1983; MacGregor, 1983). There is also evidence from interpopulation and clinical studies as well as controlled clinical trials linking diets high in Na and low in K with increased blood pressure. A major inter-population study has shown a correlation between the average Na intake and the slope of blood pressure with age, and a negative correlation between K intake and blood pressure levels (Intersalt Cooperative Research Group, 1988). These findings were confirmed and strengthened by further analysis of the available data from all studies worldwide (Department of Health and Social Security, 1992). Clinical studies in which manipulations of dietary Na and K have brought about changes in blood pressure in human elderly subjects provide further evidence (Fotherby & Potter, 1993).

### *Serum albumin*

High serum albumin levels within the normal range have been associated with reduced cardiovascular mortality and IHD in several reports (Philips *et al*. 1989; Kuller *et al*. 1991; Gillum *et al*. 1992). Protein deficiency and low serum albumin concentrations have been considered as possible initiators or factors influencing atherosclerosis (Kuller *et al*. 1991; Gillum & Makuc 1992). Low intake of animal protein has also been suggested as a risk factor for haemorrhagic stroke in Japan (Kimura *et al*. 1972). Beamer *et al*. (1993) conducted a prospective study in which three groups of subjects, assigned to a high or low albumin : globulin ratio of above or below 1·45, were followed up for an average of 1·5 (SD 0·8) years to ascertain vascular end points. Group 1 consisted of 126 patients with acute ischaemic stroke; group 2 included 109 controls matched for age and clinical risk factors for stroke; and group 3 included eighty-four healthy subjects matched for age with groups 1 and 2. The results indicated that significantly increased risk for subsequent vascular events in stroke patients, and in subjects with clinical risk factors for stroke, was associated with a prothrombotic shift in the concentrations of blood proteins, characterized by lower levels of albumin and an increased concentration of globulins and fibrinogen. Data from the first US National Health and Nutrition Examination Survey (NHANES 1) Epidemiologic Follow-up study (Gillum *et al*. 1994) were examined to assess serum albumin levels as a risk factor for stroke. White men aged 65–74 years with serum albumin concentrations of $>44$ g/l had a risk of stroke incidence over a follow-up period of 9–16 years of only about two-thirds that of men with serum albumin concentrations of $<42$ g/l. This effect persisted after controlling for multiple stroke risk variables (relative risk 0·61, 95 % CI 0·41, 0·89). A similar association with stroke death was found in white men aged 65–74 years. Serum albumin was not associated with stroke risk in white women aged 65–74 years. In black subjects aged 45–74 years, serum albumin concentrations of $>44$ g/l were associated with a risk of stroke incidence only one-half and a risk of stroke death only one-fourth that seen at levels $<42$ g/l after controlling for other risk variables.

The results of these studies and the association between serum albumin and stroke incidence and death need confirmation in further prospective randomized controlled studies. Nevertheless there is sufficient evidence to suggest that low serum albumin is strongly linked with stroke incidence and outcome. The mechanism for the effect is debatable; diets low in protein and imbalanced in their protein : energy ratios can result in low serum albumin. However, inflammatory mechanisms associated with subclinical disease are more likely to be the initiators of the low serum albumin concentrations in the large population studies of Philips *et al*. (1989), Kuller *et al*. (1991) and Gillum & Makuc (1992). The cause of low serum albumin nevertheless does not detract from its usefulness as a predictor of disease or of situations where clinical or dietary intervention might be usefully targeted.

### *Hyperhomocysteinaemia*

Hyperhomocysteinaemia may be common in the general population and has been linked with cardiovascular disease. Stroke patients frequently manifest moderate hyperhomocysteinaemia, however, this may be an acute-phase response (Lindgren *et al*. 1995). A number of studies have shown inverse relationships of blood homocysteine concentrations with plasma or serum levels of folic acid, vitamin $B_6$ and vitamin $B_{12}$ (Kang *et al*. 1987; Selhub *et al*. 1993; Robinson *et al*. 1998). Folate status is an important factor in the development of hyperhomocysteinaemia and a low serum folate concentration has been found to be a risk factor for ischaemic stroke (Giles *et al*. 1995; Molloy *et al*. 1997).

Perry *et al*. (1995) examined the association between serum total homocysteine concentration and stroke in a case–control study. Between 1978 and 1980 serum was collected from 5661 British men with no history of stroke, aged 40–59 years, randomly selected from general practice. During follow-up to December 1991, there were 141 incident cases of stroke. Serum homocysteine was also measured in 118 control men matched for age-group and town, without history of stroke at screening and who did not develop stroke or myocardial infarction during follow-up. Homocysteine concentrations were significantly higher in cases than controls. The authors also reported a graded increase in relative risk of stroke in the second, third and fourth quarters of homocysteine distribution. Adjustment for some prognostic indicators did not attenuate the association, which suggests that homocysteine is a strong and independent risk factor for stroke. In a nationally representative sample of black and white US adults (*n* 4534), Giles *et al*. (1998) found that high homocysteine concentration was independently associated with an increased likelihood of non-fatal stroke. A very recent statement for healthcare professionals on homocysteine, diet and cardiovascular disease from the Nutrition Committee, American Heart Association (Malinow *et al*. 1999) concluded that although there is considerable epidemiological evidence for

a relationship between plasma homocysteine and cardiovascular disease, not all prospective studies have supported such a relationship. Moreover, despite the potential for reducing homocysteine levels with increased intake of folic acid, it is not known whether reduction of plasma homocysteine by diet and/or vitamin therapy will reduce cardiovascular disease risk. Until results of controlled trials become available, population-wide screening is not recommended, and emphasis should be placed on meeting current recommended daily allowances for folate, as well as vitamins $B_6$ and $B_{12}$, by intake of vegetables, fruits, legumes, meats, fish, and fortified grains and cereals (Malinow *et al*. 1999).

High homocysteine may also be a risk factor for stroke in patients with sickle cell disease and systemic lupus erythematosus (Petri *et al*. 1996; Houston *et al*. 1997).

### *Dietary salt, calcium, magnesium and fibre*

Experimental and epidemiological studies have indicated that genetic–environmental or more particularly genetic–nutritional interaction is involved in the pathogenesis of hypertension and stroke. While hypercholesterolaemia is the major risk factor for atherosclerosis and myocardial infarction, hypertension and thrombosis are the major risks for both haemorrhagic and thrombotic stroke caused by arterionecrotic or arteriosclerotic lesions in intracerebral arteries. These changes have been shown to be influenced by environmental and nutritional factors. Excess salt is an important dietary factor involved in the pathogenesis of the above changes. Experimentally, excess salt intake causes hypertension not only through simple volume expansion but also through Na-accelerated vascular smooth muscle cell proliferation and enhances thrombosis by the acceleration of platelets aggregation (Yamori, 1987). Moreover, Yamori *et al*. (1994) have shown that there are also protective nutritional factors such as K, Ca, Mg, dietary fibre, protein, some amino acids and some fatty acids, which counteract the adverse effect of high Na or cholesterol intake as well as other basic pathogenic processes in hypertension, atherosclerosis and thrombosis. They also recommended well-balanced supplies of the beneficial dietary factors that are expected to aid prevention of stroke and major cardiovascular diseases by controlling hypertension, atherosclerosis, and thrombosis in men.

Ascherio *et al*. (1998) recently studied the effect of K, Mg, Ca, and dietary fibre on stroke risk among men (*n* 43 738) participating in the Health Professionals Follow-Up study. The age-adjusted relative risk of total stroke for men in the top quintile of K intake (median 4·3 g/d) compared with those in the bottom quintile (median 2·4 g/d) was 0·59 ($P = 0{\cdot}004$); the corresponding values for total dietary fibre, Mg and Ca intake were 0·57 ($P < 0{\cdot}001$), 0·62 ($P < 0{\cdot}002$) and 0·78 (NS) respectively. This study suggests that the consumption of a diet rich in K, Mg and dietary fibre is protective against stroke mortality in men. The protective effects were seen particularly in hypertensive subjects, but were observed at all levels of blood pressure and remained significant after adjustment for blood pressure level (Ascherio *et al*. 1998; Suter, 1999).

### *Dietary fat and serum lipids*

There have been conflicting reports about the relationship between dietary fat intake, serum lipids and stroke incidence (Kagan *et al*. 1985; McGee *et al*. 1985). In a large-scale multiple risk factor intervention trial, 350 977 men aged 35–57 years were followed-up for 12 years, following a single standardized measurement of serum cholesterol level and other IHD risk factors; 21 499 deaths were identified. Strong positive association was evident between serum cholesterol and death from IHD. No association was noted between serum cholesterol and stroke, but cholesterol levels $< 4{\cdot}14$ mmol/l were associated with a two-fold increase in the risk of cerebral haemorrhage and increased death from cancer of the liver and pancreas, suicide and alcohol dependence (Neaton *et al*. 1992). A recent overview of randomized trials of cholesterol-lowering and stroke incidence, which included more than 36 000 subjects failed to show a significant reduction in fatal or non-fatal stroke (Herbert *et al*. 1995). However, a recent study from Copenhagen, Denmark (Lindenstrom *et al*. 1994) in which 19 698 women and men at least 20 years old were randomly selected and followed-up for 12 years. Non-fasting plasma lipids were measured at 5-year intervals along with cardiovascular examination. Non-haemorrhagic (*n* 660) and haemorrhagic (*n* 33) strokes were recorded during the period. Total serum cholesterol was positively associated with risk of non-haemorrhagic stroke, but only for levels $>8$ mmol/l, corresponding to the upper 5 % of the distribution in the study population. Plasma triacylglycerol concentration was significantly positively associated with risk of non-haemorrhagic events and there was a negative log linear association between HDL-cholesterol and risk of non-haemorrhagic events. In a study of 832 middle-aged US men during 20 years of follow-up (The Framingham Heart Study), Gillman *et al*. (1997) found that low intakes of fat, saturated fat and monounsaturated fat were associated with reduced risk of ischaemic stroke. Meta-analysis of controlled trials in patients with hyperlipidaemia suggests that statins significantly reduce the risk of stroke by around 30 % when used in the secondary prevention of complications of atherosclerosis (Crouse *et al*. 1997; Herbert *et al*. 1997). A recent and a comprehensive review article on cholesterol and stroke (Evans & Fotherby, 1999) stated that although the association between cholesterol and stroke has been a contentious issue, more recently published studies which have considered non-haemorrhagic stroke and lipid subfractions provide more evidence for a weak relationship between these two variables, particularly an inverse association of HDL-cholesterol with non-haemorrhagic stroke. There are many confounding variables that may obscure any relationship between cholesterol and certain stroke subtypes. Further evidence of an association between stroke and cholesterol has more convincingly been demonstrated by the recent intervention trials using statins. How much of the benefit of statins is independent of cholesterol lowering is unclear but their use would seem justified in certain persons at high risk of IHD and/or stroke, particularly those with existing evidence of IHD (Evans & Fotherby, 1999).

### *Fish consumption*

High levels of fish consumption have been associated with low incidence of ischaemic stroke (Gillum *et al*. 1996), but another similar cohort study found that ischaemic stroke rates were highest in the subgroup reporting the highest fish intake (Orencia *et al*. 1996). Another recent and significant epidemiological study reported that fish consumption is associated with a reduced risk from all causes, IHD, and stroke age-standardized mortality using data from thirty-six countries (Zhang *et al*. 1999).

### *Milk consumption*

An association between milk consumption and a reduced risk of ischaemic stroke in older middle-aged men has also been reported, which could not be explained by intake of dietary Ca (Abbott *et al*. 1996).

### *Obesity*

Obesity has been found to have an independent relationship to IHD, but evidence for an association between general obesity and risk of stroke is weak. Abbott *et al*. (1994) studied 1163 non-smoking men aged 55–65 years and followed them up for 22 years. They reported that elevated BMI was associated with an increased risk of thromboembolic stroke in non-smoking men in older middle-age who are free of commonly observed conditions related to cardiovascular disease. In a study of 28 643 US male health professionals, aged 40–75 years and who had no history of stroke, during 5 years of follow-up Walker *et al*. (1996) found that abdominal obesity, but not elevated BMI, predicts risk of stroke. In another recent study from the USA, more than 12 000 adults aged 45–64 years who had no cardiovascular disease at baseline had their diabetic status measured by using fasting glucose criteria, waist and hip circumference and fasting insulin levels. During 6–8 years follow-up for ischaemic stroke occurrence, diabetes was found to be a strong risk factor. Insulin resistance, as reflected by waist : hip ratios and elevated fasting insulin levels, may also contribute to a greater risk of ischaemic stroke (Folsom *et al*. 1999).

### *Physical activity*

Regular exercise has well-established benefits for reducing the risk of premature death and other cardiovascular disease (Gorelick *et al*. 1999). The additional beneficial effect of lowering the risk of stroke has been described predominately among white subjects and is more apparent for men than women, and younger rather than older, adults (Fletcher, 1994). A dose–response relationship between increasing amounts of physical activity and the reduction in the risk of stroke has not been shown consistently. The protective effect of physical activity may be partly mediated through its role in controlling various risk factors for stroke (e.g. hypertension, diabetes and obesity), by accompanying reductions in plasma fibrinogen levels and platelet activity, and elevation in plasma tissue plasminogen activator activity and HDL concentrations (Manson *et al*. 1991; Lakka & Salonen 1993; Kokkinos *et al*. 1995; Rangemark *et al*. 1995; Wang *et al*. 1995; Blair *et al*. 1996; Williams, 1996).

### *Alcohol use*

Alcohol consumption may have a direct dose-dependent effect on the risk of haemorrhagic stroke (Donahue *et al*. 1986). For cerebral infarction, results have ranged from a definite independent effect in both men and women, an effect only in men, and no effect after controlling for other confounding risk factors such as cigarette smoking (Gorelick, 1989). A J-shaped relationship between alcohol use and ischaemic stroke has been proposed with a protective effect in light or moderate drinkers and an elevated stroke risk with heavy alcohol consumption (Gill *et al*. 1986). Alcohol may increase the risk of stroke through various mechanisms that include induction of hypertension, hypercoagulable states, cardiac arrhythmias, and cerebral blood flow reductions. There is evidence that light to moderate drinking may have beneficial effects by increasing HDL-cholesterol levels and decreasing platelet aggregation and fibrinogen levels (Thornton *et al*. 1983; Pellergrini *et al*. 1996; Gorelick *et al*. 1999). In 1998, the American Heart Association published recommendations for alcohol consumption (Biller *et al*. 1998): moderate consumption of alcohol may prevent atherosclerotic heart disease, but heavy use of alcohol should be avoided.

### *Maternal and fetal nutrition*

Recently maternal nutrition is thought to have an important influence on rates of cardiovascular diseases and their related risk factors in the next generation. The findings of an epidemiological study in London, UK, which showed that healthy and well-nourished mothers in London at the beginning of this century had children who now have low death rates from IHD and stroke, adds to this evidence (Barker *et al*. 1992). Recent findings also suggest that many human fetuses have to adapt to a limited supply of nutrients and in doing so they permanently change their physiology and metabolism. These ‘programmed’ changes may be the origins of a number of diseases in later life including IHD and the related disorders stroke, diabetes and hypertension. However, the true impact of maternal nutrition on fetal development and risk of disease in later life is not yet known and there is a need for further independent epidemiological, animal and clinical studies (Barker, 1997).

### *Genetic and racial factors*

Many diet-related chronic diseases such as diabetes, hypertension, stroke, IHD and cancer are more common amongst ethnic groups compared with whites (Bertron *et al*. 1999). For example, Qureshi *et al*. (1999) reported that African-American subjects have a two-fold increased risk for intracerebral haemorrhage compared with white subjects. Most of this risk may be explained by racial differences in systolic blood pressure and low educational attainment, which is also a risk factor for cigarette smoking and development of hypertension, obesity and high cholesterol.

Nutritional factors may have an important role to play in increased risk of stroke among ethnically and genetically different groups, however, this increased risk is more likely to be the result of complex interactions between socio-economic status, physical inactivity, limited access to health care and gene–environmental factors.

## Nutrition following the stroke

### *Acute post-stroke period*

Ill health frequently has an adverse effect on nutritional status especially in elderly people, but this is usually temporary once the customary pattern of eating is resumed. If episodes of ill health occur repeatedly or become prolonged, nutritional status may decline (Department of Health and Social Security, 1992). For stroke patients the first phase of recovery can take several weeks and continues for at least 6 months (Wade, 1992). The overall metabolic requirements in the acute or long-term post-stroke period are not well described. It is possible however to extrapolate from data describing metabolic responses during injury and stress. For example, for in-patients with head injuries, metabolic rates have been noted to increase to at least 140 % of the predicted energy expenditure for a non-injured patient. In addition, protein degradation exceeds protein synthesis, with approximately 25 % of available protein contributing to energy expenditure (Young *et al*. 1987).

### *Neurological deficit after acute stroke*

This has been discussed elsewhere (Gariballa & Sinclair, 1998). However, stroke produces an almost infinite range of possible combinations of loss of function (Wade *et al*. 1985). These deficits will have variable impact on a stroke patient's nutritional demands and actual intake. For example hemiplegia or paralysis of one half of the body can affect nutritional intake in several ways. If a patient's dominant side is affected, the patient will have to use the non-dominant hand, which will make eating difficult and tedious. Motor movement and sensory input necessary for chewing and swallowing can be affected as well in hemiplegia. During mastication, decreased sensation can cause pouching of food in the affected area without the patient being aware of it. Impaired consciousness, perceptual deficits, visual fields defects, cognitive impairment as well as motor apraxia can lead to decreased food intake and hence affect nutritional status. Dysphagia or difficulty in swallowing has obvious implications for inadequate nutritional intake. Immobility is another important factor which may affect nutritional status of stroke patients in many ways including increased protein needs due to muscle wasting, loss of Ca from bones and decubitus ulcers due to skin necrosis caused by excessive and prolonged pressure, which leads to excess N loss from the patient. Negative N balance induced by the immobility in turn increases patient's susceptibility to further skin ulceration (Mahony, 1973). Even more important is the fact that assessment, recognition and treatment of malnutrition remains a difficult problem in hospitals. The reason for this may be that nutritional assessment is not recognized as an integral part of a patient's clinical management, and for stroke patients, one of the causes of their decreased nutritional intake is that the staff looking after them are not specifically trained to assess and meet their nutritional demands.

### *Eating problems after stroke*

Many studies have demonstrated that eating problems such as anorexia, dysphagia and chewing difficulties are common in stroke patients, and that the proportion of undernourished patients was higher on discharge than on admission (Axelsson *et al*. 1984, 1989; Gariballa & Sinclair, 1998).

### *Malnutrition following acute stroke*

A number of studies have shown that a significant number of stroke patients are undernourished on admission to hospital and their nutritional status deteriorates further as an in-patient (Axelsson *et al*. 1988; Unosson *et al*. 1994). This topic has also been discussed elsewhere (Gariballa & Sinclair, 1998). However, new studies have since been published which have shown that a high proportion of stroke patients had low anthropometric and biochemical values on admission. Baseline nutritional status was worse amongst those who later died or remained in hospital compared with those discharged, and most patients who remained in hospital showed marked and significant deterioration in all measures of nutritional status within 4 weeks of hospitalization (Gariballa *et al*. 1998*a*). In another study we found that stroke patients with hypo-albuminaemia ($\leq 34$ g/l) had an increased risk of infective complications and poor functional outcome during hospitalization compared with those with normal or higher serum concentrations. Serum albumin concentrations were good predictors of the degree of disability and handicap during the hospital stay. After adjusting for poor prognostic indicators, the serum albumin concentration in hospital was a strong and independent predictor of mortality at 3 months following acute stroke (Gariballa *et al*. 1998*b*). Choi-Kwon *et al*. (1998) recently studied the nutritional status of eighty-eight female patients with first-ever strokes and 120 age-matched controls using three biochemical and five anthropometric measures. Strokes were divided into cerebral infarction (*n* 67) and intracerebral haemorrhage (*n* 21). The results suggest that undernutrition is prevalent in acute stroke patients, significantly more so in patients with intracerebral haemorrhage than in those with cerebral infarction but the authors acknowledged that this study has a number of limitations and its results should be interpreted with caution. Table 2 shows the trials which studied the prevalence of undernutrition in stroke patients in acute-care settings and its influence on outcome.

### *Nutrition status and demands during stroke rehabilitation*

Nutritional depletion during rehabilitation may be more serious than during acute illness, since rehabilitation periods may extend over weeks and months, and weight loss, although less marked than in the early catabolic phase may be greater overall. When compared with the acutely-ill,

**Table 2.** Prevalence of protein–energy undernutrition after acute stroke

| Authors and country | Subjects | Sample size (*n*) | Age (years) (mean) (SD)) | Mean LOS (SD) (d) | Time of assessments | Measurement of nutritional status | Definition of undernutrition | Endpoints | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Axelsson *et al.* (1988), Sweden | Consecutive acute stroke patients admitted to a stroke unit | 100 (sixty-four males) | 71 (8) | 13·6 | Within 4 d of admission and weekly after | TSF, MAC, weight and serum albumin, transferrin and prealbumin | Two or more nutritional measures below normal values obtained from healthy population in Sweden | Nutritional status and related variables | Sixteen (16 %) patients undernourished on admission compared with eighteen (22 %) on discharge. Undernutrition appeared to be related to infections, male sex, intake of cardiovascular drugs and high age |
| Unosson *et al.* (1994), Sweden | Acute stroke patients admitted to a neurological unit | 50 (twenty-three males) | 79 (4) | 13·8 (6·5) | Within 48 h of admission and after 2 and 9 weeks | Weight index, TSF, MAC, serum proteins (albumin, transthyretin and antitrypsin), delayed hypersensitivity, body composition (bioelectrical impedance) and functional status | If at least three were lower than the following values (including one anthropometric, serum protein and skin test). Cut-off values for men and women respectively were as follows: weight index $<80$ % and $<80$%; TSF, $\leq 6$ mm and $\leq 12$ mm; MAC, $\leq 230$ mm and $\leq 190$ mm in those aged $\leq 79$ years and $\leq 210$ mm and $\leq 180$ mm in those aged $>79$ years; transthyretin $<0{\cdot}20$ g/l and $<0{\cdot}18$ g/l; albumin 36 g/l and 36 g/l; skin test, $<10$ mm and $<10$ mm | Nutritional status and dependency | On admission four patients were undernourished. Low serum albumin and energy were common amongst stroke patients with a severely impaired functional condition. Immobility leads to loss of body cell mass |
| Davalos *et al.* (1996), Spain | Consecutive stroke patients of less than 24 h duration after the stroke | 105 (sixty-seven males) | 66 (10) | 21 (16) | Within 24 h of admission and weekly during the hospital stay | TSF, MAC, serum albumin and calorimetry | Values for each variable were expressed as a percentage of the 50th centile, adjusted for age and sex of a large sample of a healthy population living in the area | Nutritional status, morbidity and death | 16·3 % of patients undernourished at inclusion and 26·4 % after the first week. Undernourished patients showed higher stress reaction and increased frequency of infections. Undernutrition after 1 week was independently associated with increased risk of disability or death within 30 d of follow-up |
| Gariballa *et al.* (1998*a*), UK | Consecutive acute stroke patients | 201 (eighty-one males) | 77·9 (9) | Median (interquartile range): 23 (12–49) | Within 48 h of admission and after 2 and 4 weeks | Weight, TSF, BSF, MAC, AMC, albumin, transferrin, Fe, $B_{12}$ and folate | Results compared with normal values standardized for age and sex from South Wales, UK (Burr & Philips, 1984) | Nutritional status and mortality | On admission 31 % had BMI $<20$; 49 % had TSF $<25$th centile; 12 % had MAC $<25$th centile and 19 % had albumin $<35$ g/l |
| Gariballa *et al.* (1998*b*), UK | Consecutive acute stroke patients | 225 (ninety-six males) | 77·6 (9) | Median interquartile range): 23 (12–49) | Within 48 h of admission and after 2 and 4 weeks | Weight, TSF, BSF, MAC, AMC, albumin, transferrin and Fe | Results compared with normal values standardized for age and sex from South Wales, UK (Burr & Philips, 1984) | Morbidity and mortality | After adjusting for poor prognostic indicators (age, stroke severity and co-morbidity) low serum albumin at admission and during the hospital stay was a strong and independent predictor of death at 3 months after acute stroke. It also predicted poor functional status and increased morbidity |

LOS, length-of-stay; TSF, triceps skinfold thickness; MAC, mid-arm circumference; BSF, biceps skinfold thickness; AMC, arm-muscle circumference.

**Table 3.** Trials of nutritional intervention after acute stroke

| Authors and country | Subjects | Comparison | Sample size (*n*) | Age (mean (SD)) | Nutritional variables | Type and time of intervention | Endpoints | Comments |
|---|---|---|---|---|---|---|---|---|
| Nyswonger & Helmchen (1992), USA | Retrospective review of records of stroke patients admitted to a community hospital and received enteral nutrition | Patients fed within 72 h of admission (*n* 20) compared with those fed later than 72 h (*n* 32) | 52 | Range 53–95 years | According to assessment by the clinical dietitian | Enteral nutrition within or later than 72 h (not known for how long) | LOS | Significantly shorter LOS (20·1 (SD 12·9) d) in those fed within 72 h compared with those fed later than 72 h (29·8 (SD 20·1) d) |
| Norton *et al.* (1996), UK | Randomly selected stroke patients with persistent dysphagia and requiring enteral nutrition | PEG (*n* 16) *v.* NGT feeding (*n* 14) | 30 patients (eleven males) | 77 | Weight, haemoglobin, albumin and MAC | PEG compared with NGF feeding 14 d after acute stroke using a standard enteral feed (Nutrison) | Percentage of prescribed feed received, nutritional status, LOS and mortality | Significant improvement in nutritional status and shorter LOS among PEG-fed patients compared with NGT-fed group. Mortality was also significantly lower in the PEG-fed group (12 %) compared with NGT-fed group (57 %). All PEG-fed group received prescribed feed compared with 78 % of NGT-fed group |
| Davalos *et al.* (1996), Spain | Acute stroke patients within 24 h of the stroke | Nutritional status before and after feeding | 104 (sixty-seven males) | 66 (10) | TSF, MAC and serum albumin | Oral standard diet (8368 kJ and 16 g N) or polymeric enteral nutrition (126 kJ/kg and 14 g N) for dysphagic patients within 24 h of admission | Nutritional status within 1 week of hospitalization | Early enteral nutrition did not prevent malnutrition during the first week of the hospital stay |
| Gariballa *et al.* (1998*c*), UK | Stroke patients with evidence of undernutrition and without swallowing difficulties within 1 week of the stroke | Patients were randomized to 4 weeks of oral nutritional supplements plus hospital food (*n* 21) or hospital food alone (*n* 21) | 42 patients (nineteen males) | 79 (9) | Weight, TSF, MAC, albumin, transferrin and Fe | The hospital diet plus a twice daily oral nutritional supplement of ≥ 400 ml of Fortisip containing 2511 kJ and 20 g protein at 15.00 and 20.00 hours daily for 4 weeks or until death or discharge | Nutritional status, morbidity, LOS, discharge destination and mortality | Significant improvement in energy intake and nutritional status in the supplemented group compared with controls. The effect on clinical outcome amongst the supplemented group was not statistically significant however |

LOS, length of stay; PEG, percutaneous endoscopic gastrostomy; NGT, nasogastric tube; MAC, mid-arm circumference; TSF, triceps skinfold thickness.

intakes of energy and protein were lowest among long-stay and rehabilitation patients (Evans & Stock, 1971). Protein–energy malnutrition has also been found to be a strong predictor of in-hospital and 1-year post-discharge mortality in geriatric rehabilitation admissions including stroke patients (Sullivan & Walls, 1994; Sullivan *et al*. 1995).

### *Nutritional support following stroke*

Nutritional support has been found to produce clinical benefit following acute illness in some settings. A review of the literature regarding early or late nutritional support following stroke did not reveal many studies in this area (Table 3). Despite methodological limitations some studies have demonstrated that nutritional support may have a positive role to play in the care and rehabilitation of patients with acute and chronic neurological problems including stroke patients (Gariballa & Sinclair, 1998). A recent small randomized controlled single-blind trial has shown that oral nutritional supplementation significantly improved nutritional intakes, prevented decline in nutritional status and had a favourable but non-significant impact on clinical outcome after acute stroke (Gariballa *et al*. 1998*c*).

### *Nutritional status of dysphagic stroke patients*

This issue has been discussed before (Gariballa & Sinclair, 1998), however, at present, it is not known how much poor intake contributes to the poor outcome which often follows percutaneous endoscopic gastrostomy (PEG)-tube insertion, and whether improving the nutritional status before PEG-tube insertion would influence the outcome. It could also be argued that the association of increased complications and PEG-tube insertion in stroke patients is due to patient selection, since those who need the PEG-tube are those with the poorest prognosis. This important area is in need of urgent research. The Food Trial, which is a large multicentre study set up to evaluate various feeding policies in patients admitted to hospital with a recent stroke is underway and due to report after 2001.

### *Ethical aspects of percutaneous endoscopic gastrostomy-tube insertion in dysphagic stroke patients*

The decision to place a PEG-tube in a dysphagic stroke patient focuses mainly on the patient's inability to take food by mouth. Clearly, many stroke patients who receive PEG-tubes are severely disabled and some may be in the terminal phase of their illness, raising the question of the appropriateness of the intervention. Recent guidelines for PEG-tube insertion suggested that for patients who have dysphagia without other deficits in quality of life, physicians should offer and recommend the procedure. For the remaining patients who have dysphagia with other deficits in quality of life, the physician's role is to provide non-directive counselling regarding the short- and long-term consequences of a trial of PEG-tube feeding (Rabeneck *et al*. 1997). As the majority of dysphagic stroke patients will have other deficits, it is therefore the treating doctor's duty to undertake adequate consultation with competent patients, closest relatives and all members of the multidisciplinary team involved with the patient before recommending the procedure. When considering the long-term implications of the PEG-tube after discharge from hospital, the patient's social circumstances, quality of life and prognosis also have to be taken into account (Lennard-Jones, 1999).

## Conclusions and future directions

Observational studies have demonstrated that dietary factors may have an important role to play in incidence, clinical course and outcome of stroke, however, causal association is not definitely established. Therefore, there is an urgent need for further research in certain areas such as:

(1) Environmental factors, including diet may be important in the genesis of stroke and in the potential to prevent its occurrence. At present, most of this evidence in human subjects is observational and therefore does not establish a causal relationship. Large-scale experimental studies are needed to provide compelling data on which sound and scientific dietary advice to patients could be based.
(2) There is growing support for the involvement of free radicals and other micronutrients in atherosclerotic diseases such as stroke and IHD which may be associated with nutritional problems. If so, the therapeutic rewards may be great. There is a need to develop and validate better techniques for direct measurements of antioxidant capacity and oxidative stress and adjustment for confounding variables.
(3) The protective effect of intake of fruits and vegetables may not be wholly attributable to their antioxidant content. Other currently unmeasured essential nutrients may have equally protective properties. This area is in need of basic research.
(4) Despite aggressive nutritional support, it is often difficult to attenuate the catabolic response to illness or injury. Several new strategies to achieve this are under investigation. These include the administration of growth hormone to promote anabolism, and essential amino acids such as glutamine and other nutrients that can modulate immune function. Although the use of these agents has been advocated, their benefits remain controversial and further studies are needed to establish their efficacy.
(5) Energy requirements and expenditures after acute stroke and particularly during rehabilitation are of particular interest. Techniques to measure energy requirements and expenditures in these patients need to be validated.

## Recommendations on dietary and nutritional factors

### *Primary and secondary prevention of stroke*

(1) Maintain a diet that is rich in fruits and vegetables (at least five servings per d), legumes, fish, grains and cereals. For folate, as well as vitamins $B_6$ and $B_{12}$ replace deficiencies when identified. Emphasis should also be placed on meeting current recommended daily

allowances. In a high-risk patient, screening for fasting plasma homocysteine may be justified.
(2) Maintain energy balance and ideal body weight through diet and regular exercise.
(3) Limit excess intakes of saturated fat, Na and alcohol.

*Strokes in hospital and the community*

(1) Dietetic advice must be regarded as an integral part of the management of stroke patients in hospital. It should be sought early to assess the most appropriate method of meeting individual nutritional requirements in those stroke patients at risk, and provide advice for nursing and medical staff, catering and other health professionals involved.
(2) Health professionals should have access to the necessary basic training which will enable them to assess and meet the nutritional demands of stroke patients at risk of undernutrition.
(3) When considering PEG-tube feeding a dysphagic stroke patient, the treating doctor has a duty to undertake adequate consultation with the patient if competent, with the closest relatives and with all members of the multidisciplinary team involved with the patient before recommending the procedure.

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