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REVIEW

Royal College of Physicians Intercollegiate Stroke Working Party evidence-based guidelines for the secondary prevention of stroke through nutritional or dietary modification

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Abstract

Background: Each year, 15 million people worldwide and 110 000 people in England have a stroke. Having a stroke increases the risk of having another. There are a number of additional known risk factors that can be modified by diet. The present study aimed to systematically review key nutrients and diets and their role in secondary prevention, as well as provide evidence-based guidelines for use in clinical practice. The work was conducted as part of the process to develop the 4th edition of the Royal College of Physicians' (RCP) *National Clinical Guideline (NCG) for Stroke*.
Methods: Questions were generated by the research team, in consultation with the Virtual Stroke Group, an online professional interest group, and the RCP Intercollegiate Stroke Working Party Guideline Development Group. Nine questions covering several individual nutrients and diet combinations were defined and searches conducted up until 31 October 2011 using five electronic databases (Embase, Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library and Web of Science). All included studies were assessed for quality and risk of bias using van Tulder criteria for randomised controlled trials (RCTs) and Quality of Reporting of Meta-analyses (QUORUM) criteria for systematic reviews.
Results: Of 4287 abstracts were identified, 79 papers were reviewed and 29 systematic reviews and RCTs were included to provide evidence for the secondary prevention components of the guidelines. For each question, evidence statements, recommendations and practical considerations were developed.
Conclusions: This systematic review process has resulted in the development of evidence-based guidelines for use in clinical practice and has identified areas for further research.

Introduction

Stroke is a major cause of death and disability across the world. Each year, 15 million people worldwide (World Health Organization, 2004) and 152 000 people in the UK have a stroke (Townsend *et al.*, 2012a).

In 2010, stroke was the fourth largest cause of death in the UK after cancer, heart disease and respiratory disease (Townsend *et al.*, 2012b) and 300 000 people in England are living with moderate to severe disability caused by stroke (Department of Health, 2007). Having a stroke (of any kind) puts a person at increased risk of a further

event. Twenty-six percent of patients will go on to have another stroke within 5 years of the first stroke and 39% will have another stroke within 10 years (Mohan *et al.*, 2011). Prevention of stroke recurrence is focused around modification of known risk factors. Individual stroke risk factors clearly vary between individuals but are largely related to underlying pathology, comorbidities and lifestyle factors including diet (Royal College of Physicians (RCP)/Intercollegiate Stroke Working Party (ISWP), 2012). Diet types and nutrients that may influence stroke risk are summarised in Table 1.

Given the known or potential influence of diet and nutrients on stroke risk factors, there is a role for dietary modification and/or dietary supplementation in the secondary prevention of stroke. The present study aimed to systematically review the evidence of the impact of key diets and nutrients on stroke recurrence (as opposed to primary prevention) and mortality, with the aim of providing evidence-based guidelines for use in clinical practice that can be tailored to the individual.

Materials and methods

The search process started with a review of the search questions originally submitted for the 3rd edition of the *National Clinical Guidelines (NCG) for Stroke* (RCP/ISWP, 2008).

To identify other potentially relevant search questions, an e-mail was sent out to dietitians working in stroke via the Virtual Stroke Group (VSG), an online professional interest group. Search questions were developed by the search team (CH, FG, CEW), taking into account the responses received from the VSG members, using clinical judgement, expert opinion and knowledge of the evidence base. The search questions are included in Table 2.

Generic inclusion and exclusion criteria regarding participants, outcome measures and study type were

Table 1 Summary of key nutrients and diets reviewed in preparation for the 4th edition of the *National Clinical Guidelines for Stroke*

Nutrient	Influence on stroke risk	Reference
Antioxidants Vitamin A Vitamin C Vitamin E Selenium	↓ Atherosclerosis ↑ Endothelial function ↓ Platelet aggregation ↓ Blood pressure Anti-inflammatory effects	Rautianen *et al.* (2012) Del Rio *et al.* (2011) Voko *et al.* (2003)
B Vitamins Vitamin B_6 Vitamin B_{12} Folic acid	Low levels of folic acid, vitamins B_6 and B_{12} associated with ↑ serum homocysteine and ↑ risk of atherosclerosis and stroke	Homocysteine Studies Collaboration (2002) Robinson *et al.* (1998) Selhub *et al.* (1993)
Calcium	↓ Calcium intake associated with ↑ risk of hypertension	Iso *et al.* (1999) Wang *et al.* (2008)
Cardioprotective (e.g. Mediterranean diets)	Cardioprotective diets (i.e. diets low in fat and cholesterol, rich in fruits, vegetables, legumes, whole grain products and n-3 fatty acids) associated with ↓ body weight, ↓ blood pressure and serum cholesterol, have anti-inflammatory properties, decrease synthesis of cytokines, are antithrombotic and inhibit atherosclerosis	Kris-Etherton *et al.* (2001) Sofi *et al.*(2010)
Plant sterols and stanols	Plant sterols and stanols ↓ serum total and low-density cholesterol levels by suppression of dietary cholesterol absorption	Jones *et al.* (2000) AbuMweis *et al.* (2008)
Vitamin D	↓ Serum vitamin D levels associated with ↑risk of stroke Underlying mechanisms not fully understood but vitamin D may indirectly modify cardiovascular risk by its association diabetes, obesity, hypertension, smoking or cholesterol	Grandi *et al.* (2010) Poole *et al.* (2006)
Dietary fat modification MUFAs and PUFAs Saturated fats and trans fats	↑ Intakes of total fat, saturated fat and ↓ levels of PUFAs in erythrocytes associated with ↑ risk of stroke	Yu-Poth *et al.* (1999) Kris-Etherton *et al.* (1999) Boden-albala *et al.* (2009) Park *et al.* (2009)
Salt	High salt consumption or impaired excretion of salt via the kidneys can lead to hypertension. ↑ salt (sodium) intake associated with ↑ risk of stroke	Elliot (1991) Li *et al.* (2012) Gardener *et al.* (2012)

MUFA, monounsaturated fat; PUFA, polyunsaturated fat.

Table 2 Number of abstracts identified, papers reviewed, trials excluded and systematic reviews and randomised controlled trials (RCTs) included for each search question

Question	Abstracts identified	Papers reviewed	Trials excluded	Systematic reviews included	RCTs included
B1. In patients who have had a stroke, does salt reduction reduce blood pressure, stroke recurrence and mortality?	530	10	7	3	0
B2. In patients who have had a stroke, does dietary fat modification (decreased total and saturated fat; increased PUFAs and/or MUFAs) reduce stroke recurrence and mortality?	405	8	2	3	3
B3. In patients who have had a stroke, does B-vitamin or folate supplementation reduce stroke recurrence and mortality?	907	6	2	2	2
B4. In patients who have had a stroke, does antioxidant supplementation reduce stroke recurrence and mortality?	917	12	9	3	0
B5. In patients who have had a stroke, does calcium supplementation reduce stroke recurrence and mortality?	328	8	4	2	2
B6. In patients who have had a stroke, does vitamin D supplementation reduce stroke recurrence and mortality?	204	3	2	1	0
B7. In patients who have had a stroke, does consumption of a diet high in plant sterols and/or stanols reduce stroke recurrence and mortality?	237	6	6	0	0
B8. In patients who have had a stroke, do diets that are considered to be cardioprotective (e.g. Mediterranean diet, Lyon diet, DASH diet) reduce the risk of stroke recurrence and mortality?	437	21	15	0	6
B9. In patients who have had a stroke, does the inclusion of individually tailored advice on modification of dietary risk factors (in multidisciplinary interventions) reduce stroke recurrence and mortality?	322	5	3	1	1
Totals	4287	79	50	15	14

DASH, Dietary Approaches to Stop Hypertension; MUFA, monounsaturated fat; PUFA, polyunsaturated fat.

determined by the Guideline Development Group (GDG) of the RCP/ISWP and nutrition-specific criteria were determined by the authors of the present study, in collaboration with the GDG (Table 3).

Search terms were defined by the search team with the assistance of a specialist librarian (see Supporting information, Appendix S1). Searches were conducted from database origin up until 31 October 2011 by one author (FG) using five electronic databases:

- Cochrane Library
- Medline
- Embase
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- Web of Science

All titles and abstracts were reviewed by one reviewer (CH or CEW). Any potentially relevant studies identified were assessed independently by two reviewers (CEW and CH) against the inclusion criteria defined for each question using a standard pro forma developed by the search team. All potentially eligible studies were then formally evaluated by two reviewers (CEW or CH plus one additional reviewer) and any disagreements were resolved by discussion with a third person. For all included studies, data were extracted by the reviewers using a standard pro forma developed by the search team.

On the recommendation of the RCP/ISWP GDG, the risk of bias and the methodological quality of all systematic reviews were assessed using the Quality of Reporting of Meta-analyses (QUORUM) criteria (Moher *et al.*, 1999) and the quality of all randomised controlled trials (RCTs) was assessed using standard criteria (van Tulder *et al.*, 2003).

Evidence tables for each study were submitted to the GDG at regular intervals for review and final approval.

Table 3 Inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Participants	Adults aged ≥16 years Confirmed diagnosis of acute stroke	Aged <16 years Transient ischaemic attack
Interventions	Topic-specific (Table 4)	
Comparisons	Placebo or usual diet	
Outcome measures	All-cause mortality Stroke recurrence Topic-specific clinical measures (e.g. blood pressure, blood lipid levels)	
Types of study	Systematic reviews, randomised controlled trials and quasi-randomised controlled trials English language	Nonsystematic reviews, observational studies, audits, case studies

Recommendations were then written based upon the results of the included studies. In the absence of evidence from studies of sufficient quality, consensus statements were derived by the search team and submitted for final review and approval by the GDG.

The levels of evidence supporting each recommendation (related to the design of each study) and the grades of recommendation (related to the strength of the supporting evidence) were based on the criteria used by the Scottish Intercollegiate Guidelines Network (SIGN, 2010). The grading system varies from A to D, where A corresponds to the highest quality of evidence (e.g. high quality meta-analysis) and D to the lowest (e.g. expert opinion and good practice point).

The draft guidelines were reviewed during regular meetings of the full multidisciplinary RCP/ISWP throughout 2010 and 2011. The secondary prevention components were reviewed as part of the whole draft guideline document in spring 2012 by a variety of clinical and academic professionals, patient organisations and stakeholders (RCP/ISWP, 2012).

Results

Table 2 provides a summary of the number of abstracts identified, papers reviewed and the number of systematic reviews and RCTs included providing evidence for the secondary prevention components of the guidelines.

Included studies and evidence statements

Tables 4–11 provide a summary of the systematic reviews and RCTs included for each question in the guideline.

B1 In patients who have had a stroke, does salt reduction reduce blood pressure, stroke recurrence and mortality?

Two Cochrane reviews of intervention studies investigating the effects of long-term salt reduction on outcome were identified. Neither limited inclusion to patients with history of stroke because one was limited to normo- and hypertensive individuals (He & MacGregor, 2008) and the other was limited to patients with diabetic renal disease (Suckling *et al.*, 2010). Both reviews demonstrated a beneficial effect of longer term (≥4 weeks) dietary salt reduction on blood pressure but neither reported the impact on mortality or stroke recurrence. One review (He & MacGregor, 2008) demonstrated a correlation between the magnitude of salt reduction and the magnitude of blood pressure reduction. One other Cochrane review evaluating the specific effect of dietary advice on cardiovascular risk factors (Brunner *et al.*, 2009) was identified. This review demonstrated that dietary advice significantly reduces both systolic and diastolic blood pressure. This evidence further suggests there is benefit in long-term dietary salt reduction on blood pressure; the effects on stroke recurrence and mortality are, however, yet to be determined. The moderate to high heterogeneity across studies included in both reviews, and the fact that the majority of studies included were relatively small and of short duration, suggests the results should be interpreted with caution. In collaboration with the GDG, the following evidence statement was developed:

B1.1 All patients, but especially people with hypertension, should be advised to reduce their salt intake by:

Not adding salt to food at the table.
Using as little salt as possible in cooking.
Avoiding high-salt foods (e.g. processed meat products, such as ham and salami, cheese, stock cubes, preprepared soups and savoury snacks such as crisps and salted nuts) (RCP/ISWP, GRADE A).

B2 In patients who have had a stroke, does dietary fat modification (decreased total and saturated fat; increased polyunsaturated fats (PUFAs) and/or monounsaturated fats reduce stroke recurrence and mortality?

One Cochrane review (Hooper *et al.*, 2011), one systematic review (Marik & Varon, 2009) and two large RCTs (Valagussa *et al.*, 1999 and Tanaka *et al.*, 2008) investigating the effects of dietary fat modification on cardiovascular risk factors met the inclusion criteria. A further RCT investigating the effects of B-vitamins and PUFAs on cardiovascular disease in patients with a history of ischaemic heart disease or stroke, the Su.Fol.OM3 trial (Galan *et al.*, 2010), was reviewed. One other Cochrane review evaluating the specific effect of dietary advice

Table 4 Description of studies included for question B1: in patients who have had a stroke, does salt reduction reduce blood pressure, stroke recurrence and mortality?

Study	Study design	Participants	Study details	Results	Comments
He & MacGregor (2008)	*Cochrane review* Systematic review and meta-analysis of RCTs	*Normotensives* 11 trials (n = 2220) Hypertensives 20 trials (n = 802)	*Intervention:* Advice and support on modest dietary salt reduction *Control:* Usual salt intake *Duration:* Interventions ≥4 weeks	Normotensives *Systolic:* −2.31 mmHg (95% CI −3.48, −1.14) *Diastolic:* NS Hypertensives *Systolic:* −5.27 mmHg (95% CI −6.69, −3.85) *Diastolic:* −2.76 mmHg (95% CI: −3.55, −1.97)	Moderate to high heterogeneity observed across studies No details on the proportion of primary to secondary prevention studies
Suckling *et al.* (2010)	*Cochrane review* Systematic review and meta-analysis of RCTs	13 Trials (n = 254) Adults with diabetes Type 1 n = 75 Type 2 n = 158	*Intervention:* Low salt intake (quantity not specified) *Control:* High salt intake (quantity not specified) *Duration:* Not specified – reported median duration of salt restriction was 1 week	Type 1 diabetes *Systolic:* −7.11 mmHg (95% CI: −9.13, −5.10) *Diastolic*: −3.13 mmHg (95% CI: −4.28, −1.98) Type 2 diabetes *Systolic*: NS *Diastolic:* −2.87 mmHg (95% CI: −4.39, −1.35)	High heterogeneity observed across trials No details on the proportion of primary to secondary prevention studies
Brunner *et al.* (2009)	*Cochrane review* Systematic review and meta-analysis of RCTs	38 Trials (n = 17 871) RCTs in healthy adults, some with CVD	*Intervention:* Dietary advice to reduce CVD risk including reduction in salt intake *Control:* Minimal or no dietary advice *Duration:* Median 10 months (range 3 months to 4 years)	Total population *Systolic*: −2.07 mmHg (95% CI: −3.19, −0.95) *Diastolic*: −1.15 mmHg (95% CI: −1.85, −0.46) General study population (not at high CVD risk) *Systolic:* NS *Diastolic:* NS CVD high risk *Systolic:* −1.96 mmHg (95% CI: −3.41, −0.51) *Diastolic:* −1.46 mmHg (95% CI: −2.62, −0.31)	Low to moderate heterogeneity observed across studies Advice delivered in a variety of ways (e.g. one-to-one, group sessions and written materials) Considerable variation in intensity and duration of interventions

CI, confidence interval; CVD, cardiovascular disease; NS, nonsignificant; RCT, randomised controlled trial.

Table 5 Description of studies included for question B2: in patients who have had a stroke, does dietary fat modification (decreased total and saturated fat; increased PUFAs and/or MUFAs) reduce stroke recurrence and mortality?

Study	Study design	Participants	Study details	Results	Comments
Hooper *et al.* (2011)	*Cochrane review* Systematic review and meta-analysis	48 trials (n = 65 978) Adults at any risk of CVD	*Intervention:* Dietary modification [i.e. dietary advice, dietary supplementation (of fats, oils or modified or low-fat foods) or a provided diet] *Control:* Usual diet, placebo or a control diet *Duration:* At least 6 months	Primary outcome *Cardiovascular mortality*: NS Secondary outcomes *Total mortality:* NS *Cardiovascular events*: RR: 0.86 (95% CI: 0.77, 0.96) *Myocardial infarction*: NS *Stroke:* NS	Low to moderate heterogeneity observed across studies No details on the proportion of primary to secondary prevention studies
Marik & Varon (2009)	Systematic review and meta-analysis	11 trials (n = 39 044)	*Intervention* Dietary supplements of EPA and DHA *Control* Placebo (three studies used olive oil and two used sunflower seed oil, unspecified in six trials) *Duration* At least 1 year	*Cardiovascular deaths:* OR: 0.87 (95% CI: 0.79–0.95) *Sudden cardiac death:* OR: 0.87 (95% CI: 0.76–0.99) *All-cause mortality:* OR: 0.92 (95% CI: 0.85–0.99) *Nonfatal cardiovascular events:* OR: 0.92 (95% CI: 0.85–0.99)	Low to moderate heterogeneity observed across studies No details on the proportion of primary to secondary prevention studies Doses of EPA/DHA varied and studies used different placebos
Valagussa *et al.* (1999)	Four-arm multicentre RCT (GISSI Trial)	n = 11 324 Adults with a recent history (≤3 months) of MI	*Intervention 1:* n-3 PUFA (1 g per day) *Intervention 2:* Vitamin E (300 mg per day) *Intervention 3:* Omega-3 PUFA (1 g per day) + vitamin E (300 mg per day) *Control:* No supplementation *Duration:* 3.5 years	*Death, nonfatal MI, and nonfatal stroke*: RR: 0·90 (95% CI: 0·82, 0·99) *Cardiovascular death, nonfatal MI, and nonfatal stroke*: NS *Cardiovascular deaths:* RR: 0·83 (95% CI: 0·71, 0·97) *Fatal and nonfatal stroke*: NS	
Tanaka *et al.* (2008)	Two-arm RCT (secondary analysis of the JELIS trial (Yokohama *et al.*, 2007))	Primary prevention n = 17 703 Secondary prevention n = 942 Adults with serum total cholesterol ≥6.5 mM	*Intervention:* EPA (1800 mg per day) with statin *Control:* Statin alone *Duration:* 5 years	Primary prevention *Total stroke events: NS* Secondary prevention *Total stroke events:* HR 0.80 (95% CI: 0.64, 0.997)	

Table 5 *(Continued)*

Study	Study design	Participants	Study details	Results	Comments
Galan *et al.* (2010)	Multicentre (n = 257) four-arm RCT (PUFA arm of Su.Fol.OM3 trial)	n = 2501 Secondary prevention trial in adults within 12 months of a diagnosis of an acute coronary event or cerebral ischaemic event	*Intervention* (n = 633) Omega-3 fatty acid supplement (600 mg of EPA and DHA at a ratio of 2 : 1) *Control* Placebo (n = 626) *Duration* 5 years (median 4.7 years)	Primary outcome *Major cardiovascular events*: *NS* Secondary outcomes *Nonfatal myocardial infarction:* *NS* *All coronary events*: NS *Stroke*: NS *All cerebrovascular events*: NS *All revascularisations*: NS *Other cardiovascular events*: NS *All deaths*: NS	

CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HR, hazard ratio; MUFA, monounsaturated fatty acid; MI, myocardial Infarction; NS, nonsignificant; OR, odds ratio; RR, relative risk; PUFA, polyunsaturated fatty acid; RCT, randomised controlled trial.

on cardiovascular risk factors (Brunner *et al.*, 2009) was identified.

One Cochrane review (Hooper *et al.*, 2011) concluded that there was a small but potentially important reduction in cardiovascular risk from the modification of dietary fat but not the reduction of total fat, in longer trials (≥6 months). There were no clear effects of changes in dietary fat intake on all-cause or cardiovascular mortality. Stroke events were included as part of a composite outcome in this review and therefore it is not possible to determine the specific effect of these interventions on stroke recurrence. The systematic review (Marik & Varon, 2009) suggested a beneficial effect of PUFAs on all-cause mortality and cardiovascular events (including three secondary prevention trials) but stroke-specific outcomes were not reported. Valagussa *et al.*, 1999 reported effects of vitamin E, PUFAs, vitamin E + PUFAs versus controls on all-cause mortality, stroke (included in cardiovascular deaths) and cardiovascular events in post-myocardial infarction (MI) patients. This trial suggested a beneficial effect of PUFAs on the risk of fatal and nonfatal strokes. It should be noted, however, that subjects were already on a Mediterranean-type diet (therefore with a higher fish, fruit and vegetable and olive oil intake than the UK population). Tanaka *et al.*, 2008; investigated the effects of PUFAs on stroke recurrence and cardiovascular events in a hyper-cholesterolaemic, Japanese population. The study did not report on all-cause or stroke mortality. Tanaka *et al.*, 2008 found a significant, beneficial effect of PUFAs on stroke recurrence; however, it should be noted that subjects had a higher total fish intake than the general UK population. In the PUFA arm of the Su.Fol.OM3 trial (Galan *et al.*, 2010), supplementation with omega-3 fatty acids had no significant effect on major vascular events and no effect on stroke events. Doses of eicosapentaenoic acid/docosahexaenoic acid varied between studies and different studies used different placebos. It is not therefore possible to make evidence-based recommendations on dose.

A Cochrane review evaluating the effects of dietary advice on cardiovascular risk factors (Brunner *et al.*, 2009) concluded that dietary advice results in significant reductions in total and saturated fat intake. The effects of intervention on stroke recurrence and mortality were not investigated in this review. In conclusion, although there is some evidence of benefit from increasing dietary intake of PUFAs in the secondary prevention of stroke in subjects consuming a Mediterranean-style diet, it is not clear whether the benefits would be evident in subjects consuming a UK-style diet. After discussion with the GDG, the following evidence statement was developed:

B2.1 All patients should be advised to reduce and replace saturated fats in their diet with polyunsaturated or monounsaturated fats by:

Table 6 Description of studies included for Question B3: in patients who have had a stroke, does B-vitamin or folate supplementation reduce stroke recurrence and mortality?

Study	Study design	Participants	Study details	Results	Comments
Marti-Carvajal *et al.* (2009)	*Cochrane review* Systematic review and meta-analysis	Eight trials (n = 24 210) Adults at risk or with established CVD with at least 1 year follow-up	*Intervention:* Vitamin B_6 (0–50 mg per day); B_9 (0–5 mg per day); B_{12} (0–1 mg per day) *Control:* Placebo or usual care *Duration:* Variable (often not reported)	*All-cause mortality:* NS *Stroke*: NS *MI:* NS	Low heterogeneity across studies No details on the proportion of primary to secondary prevention studies
Bazzano *et al.* (2006)	Meta-analysis of eight secondary prevention RCTs	Eight trials (n = 16 958) Patients with pre-existing CVD or renal disease	*Intervention:* Folic acid supplementation *Control:* Placebo or usual care *Duration:* 6–60 months	*Stroke:* NS *CVD*: NS *CHD*: NS *All-cause mortality*: NS	Variable doses of folic acid
Galan *et al.* (2010) (Su.Fol.OM3 trial)	Multicentre four-arm RCT (B-vitamin arm of Su.Fol.OM3 trial)	n = 2501 (257 centres) Secondary prevention trial in adults within 12 months of a diagnosis of an acute coronary event or cerebral ischaemic event	*Intervention:* Dietary supplement of vitamin B complex *Control:* Placebo (n = 626) *Duration:* 5 years (median 4.7 years)	*Major cardiovascular events*: NS *Stroke events:* HR 0.57 (95% CI: 0.33, 0.97) *Death from cardiovascular causes*: NS *Death from all causes*: HR 1.55 (95% CI: 1.07, 2.25) *MI*: NS	
Hankey *et al.* (2010) (VITATOPS Trial)	Multicentre secondary prevention RCT	n = 8164 (123 centres) Secondary prevention trial in patients with a recent history stroke or TIA	*Intervention:* Dietary supplement of vitamin B complex (folic acid 2 mg; B_6 – 25 mg; B_{12} – 0.5 mg) *Control:* Placebo (n = 4075) *Duration:* Variable	Primary outcome *Stroke, MI or vascular death*: NS Secondary outcomes *Stroke*: NS *MI*: NS *Vascular death*: RR: 0.86 (95% CI: 0.75, 0.99) *Nonvascular death*: NS *Death from any cause*: NS	N.B. This paper includes a meta-analysis of RCTs (see below)
Hankey *et al.* (2010) (meta-analysis)	Meta-analysis of 15 RCTs	15 RCTs (n = 49 112) Primary and secondary prevention trials	*Intervention:* B-vitamin supplementation or high dose B-vitamins *Control:* Placebo, usual care or low-dose B-vitamins *Duration:* Not specified	*Nonfatal stroke, nonfatal MI, or death as a result of vascular causes*: NS *Stroke*: NS *MI*: NS	Low heterogeneity across studies

CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; NS, nonsignificant; RCT, randomised controlled trial; RR, relative risk; TIA, transient ischaemic attack.

Table 7 Description of studies included for Question B4: in patients who have had a stroke, does antioxidant supplementation reduce stroke recurrence and mortality?

Study	Study design	Participants	Study details	Results	Comments
Alkhenizan & Al-Omran (2004)	Systematic review and meta-analysis	Nine RCTs (n = 80 645) Adults at any given risk of CVD (with or without existing CVD)	*Intervention:* Vitamin E supplement (50–800 mg per day) *Control:* Placebo or usual care *Duration:* 510 days to 8 years	Primary prevention *Nonfatal MI*: NS *Stroke:* NS Secondary prevention *Total MI:* NS *Fatal MI:* NS *Nonfatal MI:* RR: 0.51 (95% CI: 0.38, 0.70) *All stroke:* NS *Ischemic stroke:* NS *Haemorrhagic stroke:* NS *Total mortality*: NS	Considerable variation in trial size, dose and duration of intervention
Bin *et al.* (2011)	Systematic review and meta-analysis	13 RCTs (n = 166 282) Healthy, at risk or adults with established CVD	*Intervention:* Vitamin E (50–800 mg per day) alone; Vitamin E or aspirin; Vitamin E or β-carotene; Vitamin E or vitamin C or β-carotene; Vitamin E or PUFA; Vitamin E or vitamin C *Control:* Placebo *Duration:* 510 days to 10 years	*All stroke*: NS *Ischaemic stroke*: NS *Haemorrhagic stroke*: NS *Fatal stroke*: NS *Nonfatal stroke*: NS	Considerable variation in trial size, dose, duration of intervention and comparison groups
Eidelman *et al.* (2004)	Systematic review and meta-analysis	Seven RCTs (n = 80 395) Healthy, at risk or patients with CVD (two trials included patients undergoing secondary prevention)	*Intervention:* Vitamin E (30–800 mg per day) *Control:* Placebo *Duration:* 3–6 years	*Cardiovascular events*: NS *Cardiovascular death*: NS *Nonfatal MI*: NS *Nonfatal stroke*: NS *Ischaemic stroke*: NS *Haemorrhagic stroke*: NS	

CI, confidence interval; CVD, cardiovascular disease; MI, myocardial infarction; PUFA, polyunsaturated fatty acids; NS, nonsignificant; RCT, randomised controlled trial; RR, relative risk.

Using low-fat dairy products.

Replacing butter, ghee and lard with products based on vegetable and plant.

Oils.

Limiting red meat intake, especially fatty cuts and processed forms (RCP/ISWP, GRADE A).

B3 In patients who have had a stroke, does B-vitamin or folate supplementation reduce stroke recurrence and mortality?

One Cochrane review (Marti-Carvajal *et al.*, 2009), a meta-analysis (Bazzano *et al.*, 2006) and two large RCTs [Su.Fol.OM3 trial (Galan *et al.*, 2010) and VITAmins TO Prevent Stroke (VITATOPS) (Hankey *et al.*, 2010)] were identified.

The Cochrane review (Marti-Carvajal *et al.*, 2009) concluded that currently there is no evidence to support the use of B-vitamin supplementation as a homocysteine-lowering intervention to prevent cardiovascular events. The meta-analysis (Bazzano *et al.*, 2006) showed no significant benefit of folic acid supplementation on cardiovascular outcomes or all-cause mortality. The B-vitamin arm of the Su.Fol.OM3 trial (Galan *et al.*, 2010) reported that B-vitamin supplementation resulted in lower median plasma homocysteine at 1 year and at end of trial. However, B-vitamin supplementation was not associated with a significant effect on the composite number of cardiovascular events. Although those on B-vitamins had significantly fewer stroke events (P = 0.04), B-vitamin supplementation was associated with a significantly higher risk of death from any cause.

The VITATOPS trial (Hankey *et al.*, 2010) was a secondary prevention trial where subjects were supplemented with folic acid and B-vitamins. This trial suggested that B-vitamins were no more effective than placebo at reducing the incidence of major vascular events or death from any cause. B-vitamin supplementation was, however,

Table 8 Description of studies included for question B5: in patients who have had a stroke, does calcium supplementation reduce stroke recurrence and mortality?

Study	Study design	Participants	Study details	Results	Comments
Bolland *et al.* (2010) (meta-analysis)	Systematic review and meta-analysis	15 RCTs Five RCTs included patient level data (n = 815) 10 RCTs included trial level data (n = 11 921)	*Intervention:* Calcium supplementation ≥500 mg per day *Control:* Placebo *Duration:* >1 year	Patient level data *MI*: HR 1.31, 95% CI = 1.02–1.67, P = 0.035 *Stroke*: NS *Death*: NS *MI, stroke or sudden death*: NS Trial level data *MI*: RR: 1.27 (95% CI: 1.01–1.59, P = 0.038) *Stroke*: NS	Co-administration of calcium and vitamin D were not considered
Bolland *et al.* (2011)	Meta-analysis of 9 RCTs (including re-analysis using part of the WHI Trial)	Nine RCTs *Analysis A (patient level data)* Three trials (n = 20 090) *Analysis B (trial level data)* Nine trials (n = 28 072)	*Intervention/Control* *A* Calcium and vitamin D (variable doses) versus Placebo *B* Calcium supplements with or without vitamin D (variable doses) *Duration:* Not specified	Analysis A *MI*: RR: 1.21 (95% CI: 1.01–1.44, P = 0.04) *Stroke*: RR: 1.20 (95% CI: 1.00–1.43, P = 0.05) *MI or Stroke*: RR: 1.16 (95% CI: 1.02–1.32, P = 0.02) *Death (All causes):* NS Analysis B *MI*: RR: 1.24 (95% CI: 1.07–1.45, P = 0.004) *Stroke*: RR: 1.15 (1.00–1.32, P = 0.06) *MI or stroke*: RR: 1.15 (1.03–1.27, P = 0.009) *Death (all causes):* NS	WHI study was on post-menopausal women only
LaCroix *et al.* (2009)	Double-blind multicentred RCT WHI Trial	n = 36 282 Post-menopausal women aged 51–82 years	*Intervention:* Calcium 1000 mg plus 400 IU vitamin D_3 Supplementation *Control:* (n = 18 106) Placebo *Duration:* Mean 7.0 years	*Total mortality:* NS *Stroke:* NS *CHD:* NS *Cancer:* NS	WHI study was on post-menopausal women only
Hsia *et al.* (2007)	Double-blind multicentred RCT WHI Trial	n = 36 282 Post-menopausal women aged 50–79 years History of previous stroke at baseline not specified	*Intervention:* Calcium carbonate 500 mg with vitamin D_3 200 IU twice daily *Control:* (n = 18 106) Placebo *Duration:* Mean 7.0 years	*MI or CHD death*: NS *Stroke*: NS *Composite outcomes*: NS Subgroup analysis indicated women with fewer risk factors were at higher stroke risk with calcium/vitamin D supplementation (P = 0.02)	The original study was designed to evaluate effects of intervention on fracture risk not CV outcomes

CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IU, international units; MI, myocardial infarction; NS, nonsignificant; RCT, randomised controlled trial; RR, relative risk; WHI, Women's Health Initiative trial.

Table 9 Description of studies included for question B6: in patients who have had a stroke, does vitamin D supplementation reduce stroke recurrence and mortality?

Study	Study design	Participants	Study details	Results	Comments
Elamin *et al.* (2011)	Systematic review and meta-analysis	51 RCTs Adults with or without existing CVD	*Intervention:* Vitamin D supplements or vitamin D + calcium supplements or food rich in vitamin D (e.g. cod liver oil) *Control:* Placebo or calcium supplements or normal diet or nothing *Duration:* Variable (up to 108 months)	*Stroke:* NS *Mortality:* NS *MI:* NS *Change in blood lipids, blood glucose, and BP measurements:* NS	No details on the proportion of primary to secondary prevention studies Trials used different quantities, frequencies and types of vitamin D

BP, blood pressure; CVD, cardiovascular disease; MI, myocardial infarction; NS, nonsignificant; RCT, randomised controlled trial.

associated with a significant reduction in death from specifically vascular causes. In conclusion, the effects of B-vitamin and folate supplementation on stroke recurrence and mortality are inconsistent and merit further research. Low heterogeneity was observed across studies in both the Cochrane review (Marti-Carvajal *et al.*, 2009) and the VITATOPS trial (Hankey *et al.*, 2010). The following evidence statement was developed:

> B3.1 The following interventions have not been shown to reduce stroke re-occurrence:
> vitamin B and folate supplementation (RCP/ISWP, GRADE A).

B4 In patients who have had a stroke, does antioxidant supplementation reduce stroke recurrence and mortality?

Two meta-analyses (Alkhenizan & Al-Omran, 2004; Bin *et al.*, 2011) and one systematic review (Eidelman *et al.*, 2004) met the inclusion criteria. All identified studies evaluated the effects of vitamin E supplementation.

One meta-analysis (Alkhenizan & Al-Omran, 2004) concluded that vitamin E supplementation was not associated with a reduction in total mortality or total cardiovascular mortality, although it was associated with a small, (3%) absolute reduction in nonfatal MI in patients with pre-existing coronary artery disease. The systematic review (Eidelman *et al.*, 2004) concluded there were no significant effects of vitamin E supplementation on any cardiovascular endpoint including nonfatal MI and stroke. A newer meta-analysis (Bin *et al.*, 2011) focused on primary prevention of stroke and showed no benefit of vitamin E supplementation in the prevention of stroke of any type (including fatal). In conclusion, there is no evidence of benefit from vitamin E supplementation in the prevention of stroke or re-stroke.

No specific evidence statement was developed for this question because the guideline already included a recommendation that all patients should be advised to eat the optimum diet, including foods high in anti-oxidants (i.e. fruit and vegetables) (RCP/ISWP, GRADE A).

B5 In patients who have had a stroke, does calcium supplementation reduce stroke recurrence and mortality?

One meta-analysis (Bolland *et al.*, 2010), one reanalysis of the Women's Health Initiative (WHI) dataset and meta-analysis (Bolland *et al.*, 2011) and two RCTs of calcium plus vitamin D supplementation in post-menopausal women (Hsia *et al.*, 2007; LaCroix *et al.*, 2009) were identified. Both meta-analyses (Bolland *et al.*, 2010, 2011) suggested calcium supplementation was associated with an increased risk of cardiovascular events with a nonsignificant increase in the risk of stroke (Bolland *et al.*, 2010). One RCT (Hsia *et al.*, 2007) reported no effect of calcium and vitamin D supplementation on the risk of stroke or MI. The other RCT (LaCroix *et al.*, 2009) reported no effect of calcium and vitamin D supplementation on the risk of cerebrovascular or cardiovascular death. In conclusion, self-supplementation with calcium is not recommended in post-menopausal women as a result of the increased risk of cardiovascular events and stroke. The role of prescribed calcium supplementation (with or without vitamin D) in the risk of re-stroke has yet to be determined. The following evidence statement was developed:

> B5.1 The following interventions have not been shown to reduce stroke re-occurrence:
> supplementation with calcium with or without vitamin D (RCP/ISWP, GRADE A).

B6 In patients who have had a stroke, does vitamin D supplementation reduce stroke recurrence and mortality?

One meta-analysis (Elamin *et al.*, 2011) was identified. This review consisted mainly of primary prevention trials and reported no effect of vitamin D supplementation on all-cause mortality, MI or stroke events. Subgroup analysis of vitamin D deficient subjects also showed no

Table 10 Description of studies included for question B8: in patients who have had a stroke, do cardioprotective diets reduce stroke recurrence and mortality?

Study	Study design	Participants	Study details	Results	Comments
Appel *et al.* (1997)	RCT (DASH trial*)	*n* = 459 Healthy adults aged ≥22 years; systolic BP <160 mmHg; diastolic BP 80–95 mmHg	*Intervention* (1) Fruits-and-vegetables diet: control diet with more fruits and vegetables (2) DASH diet*: rich in fruits, vegetables, and low-fat dairy foods *Control:* Typical diet of a substantial number of Americans *Duration:* 8 weeks	DASH diet* *Systolic*: –5.5 mmHg (*P* = 0.001) *Diastolic*: –3.0 mmHg (*P* = 0.001) Fruits-and-vegetables diet *Systolic:* –2.8 mmHg (*P* = 0.001) *Diastolic:* –1.1 mmHg (*P* = 0.07) In those with hypertension (*n* = 133) DASH* versus control diet *Systolic:* –11.4 mmHg (*P* = 0.001) *Diastolic:* –5.5 mmHg (*P* = 0.001)	Effects of interventions on stroke recurrence and mortality were not evaluated
Appel *et al.* (2003)	Multicentre RCT	810 participants, healthy adults with above-optimal BP	*Intervention* (1) 'Established' = behavioural intervention (e.g. increase physical activity) (2) 'Established plus DASH'* = 'Established' intervention + DASH diet* *Control:* Advice only (*n* = 273) *Duration:* 6 months	*Systolic:* –3.7 mmHg (P < 0.001) in the Established group *Systolic:* –4.3 mmHg (P < 0.001) in the Established plus DASH group	Effects of interventions on stroke recurrence and mortality were not evaluated
Howard *et al.* (2006)	RCT	*n* = 48 835 Post-menopausal women aged 50–79 years, some with CVD	*Intervention* (*n* = 19 541) Intensive behaviour modification in group and individual sessions designed to ↓ total fat intake and ↑ intakes of vegetables/fruits and grains *Control* (*n* = 29 294) Diet-related education materials *Duration* Mean follow-up: 8 years	*CHD, stroke, or CVD*: NS Significant decreases in body weight, waist circumference, diastolic BP and LDL cholesterol (*P* < 0.001 at year 3 for all)	
Fung *et al.* (2008)	Prospective cohort	*n* = 88 517 female nurses aged 34–59 years	Explored association between DASH* diet and risk of CHD and stroke in women Diet assessed seven times during 24 years of follow-up. DASH score based on eight food and nutrient components was calculated. Participants were divided into quintiles of intake *Duration:* 24 years	Effect of top quintile of the DASH score, compared with the bottom quintile *Nonfatal and fatal CHD:* RR: 0.76 (95% CI: 0.67–0.85, *P* < 0.001) *Total stroke:* RR: 0.82 (95% CI: 0.71–0.94, *P* = 0.002)	
Giannuzzi *et al.* (2008)	Multicentre RCT (GOSPEL Trial)	3241 participants Previous MI (no information on previous strokes)	*Intervention* (*n* = 1620) Long-term, reinforced, multifactorial educational and behavioural intervention (e.g. to give up smoking and adopt a Mediterranean-style diet) *Control* (*n* = 1621): Usual care *Duration:* 3 years	*Primary endpoint:* NS *Stroke:* NS *Mortality:* NS *Mortality plus nonfatal MI and stroke:* HR = 0.67 (95% CI: 0.47–0.95) *Cardiac death plus nonfatal MI:* HR = 0.64 (95% CI: 0.43–0.94) *Nonfatal MI:* HR = 0.52 (95% CI: 0.31–0.86)	

Table 10 *(Continued)*

Study	Study design	Participants	Study details	Results	Comments
Chow *et al.* (2010)	Multicentre RCT 'OASIS Trial'	18 809 participants Acute coronary syndrome (MI or unstable angina), aged ≥60 years	Data collected on patient-reported lifestyle behaviours at 30-day follow-up visit; divided into groups according to smoking status and diet/exercise program adherers *Duration:* 6 months	Effect of persistent smoking and non-adherence to diet and exercise versus never smokers who modified diet and exercise *MI, stroke or death:* RR: 3.8 (95% CI: 2.5–5.9) Effect of diet and exercise versus no diet/exercise *Stroke:* RR: 0.46 (95% CI: 0.26–0.82) *Death:* RR: 0.45 (95% CI: 0.33–0.60)	

CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; LDL, low-density lipoprotein; MI, myocardial infarction; NS, nonsignificant; RCT, randomised controlled trial; RR, relative risk.
*Dietary Approaches to Stop Hypertension (DASH): a dietary pattern high in fruits and vegetables, moderate in low-fat dairy products and low in animal protein but with a substantial amount of plant protein from legumes and nuts.

Table 11 Description of studies included for question B9: in patients who have had a stroke, does the inclusion of individually tailored advice on modification of dietary risk factors reduce stroke recurrence and mortality?

Study	Study design	Participants	Study details	Results	Comments
Brunner *et al.* (2009)	*Cochrane review* Systematic review and meta-analysis	38 RCTs (n = 17 871) participants/clusters Healthy adults, some with CVD (<25% of study participants)	*Intervention:* Dietary advice to reduce cardiovascular risk *Control:* Minimal or no dietary advice *Duration:* At least 3 months (median 10 months)	*Total serum cholesterol*: –0.16 mM (95% CI: 0.06 to 0.25) *Serum LDL cholesterol:* –0.18 mM (95% CI: 0.1 to 0.27)	Low to moderate heterogeneity observed across studies Considerable variation in intensity and duration of interventions
Ma *et al.* (2009)	RCT	n = 419 Adults with or without existing CVD, who had major modifiable CV risk factors	*Intervention:* One-on-one nurse- and dietitian-led intervention *Control:* Routine medical care *Duration:* Target of eight to 10 visits during 15 months	Framingham risk score 0.92 (intervention) 0.19 (control) P = 0.001 Systolic BP 4.2 mmHg (intervention) 2.6 mmHg (control) P = 0.003 Diastolic BP 6 mmHg (intervention) 3 mmHg (control) P = 0.02	

BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; LDL, low-density lipoprotein; MI, myocardial infarction; NS, nonsignificant; RCT, randomised controlled trial; RR, relative risk.

effect of supplementation on outcomes. There is a lack of evidence to support the role of vitamin D supplementation in the secondary prevention of stroke recurrence. The following evidence statement was developed:

B6.1 The following interventions have not been shown to reduce stroke re-occurrence:

supplementation with calcium with or without vitamin D (RCP/ISWP, GRADE A).

B7 In patients who have had a stroke, does consumption of a diet high in plant sterols and/or stanols reduce stroke recurrence and mortality?

No intervention studies met the criteria for this question; therefore, there is a lack of evidence to support any recommendation regarding the use of plant stanols and/or sterols to prevent stroke recurrence. Therefore, no evidence statement was developed. One meta-analysis evaluated the impact of plant sterols and stanols on serum cholesterol levels, and found that plant sterol containing products significantly reduced low-density lipoprotein (LDL) cholesterol compared to placebo, although the effect was related to individual's baseline LDL, the food carrier and frequency and time of intake (AbuMweis *et al.*, 2008).

B8 In patients who have had a stroke, do cardioprotective diets [e.g. Mediterranean diet, Lyon diet, Dietary Approaches to Stop Hypertension (DASH) diet] reduce stroke recurrence and mortality?

Six RCTs were identified (Appel *et al.*, 1997, 2003; Howard *et al.*, 2006; Fung *et al.*, 2008; Giannuzzi *et al.*, 2008; Chow *et al.*, 2010).

The WHI Dietary Modification Trial was a randomised controlled trial in 48 835 post-menopausal women (Howard *et al.*, 2006). The intervention consisted of intensive behaviour modification in group and individual sessions designed to reduce total fat intake, increase fruit and vegetables intake to five servings a day and grains intake to at least six servings a day. Over a mean of 8.1 years, the intervention failed to significantly reduce the risk of coronary heart disease (CHD), stroke, or cardiovascular disease and achieved only modest effects on cardiovascular risk factors. The DASH diet (Appel *et al.*, 1997) has been shown to lower both systolic and diastolic blood pressure substantially. The diet is high in fruits and vegetables, moderate in low-fat dairy products, and low in animal protein but with a substantial amount of plant protein from legumes and nuts. A long-term follow-up study (up to 24 years) demonstrated that adherence to a DASH-style diet is associated with a lower risk of CHD and stroke among middle-aged women (Fung *et al.*, 2008).

The Global Secondary Prevention Strategies to Limit Event Recurrence (GOSPEL study) was a multicentre, randomised controlled trial in 3241 post-MI patients, comparing a long-term, reinforced, multifactorial educational and behavioural intervention (including adopting a Mediterranean-style diet) with usual care (Giannuzzi *et al.*, 2008). The intervention resulted in a decreased risk of cardiovascular mortality, nonfatal MI and stroke; however, it was not possible to determine the specific effect of dietary modification.

A study reporting on adherence to diet, physical activity and smoking cessation at 30-day follow-up (Chow *et al.*, 2010) reported on cardiovascular events (MI, stroke, cardiovascular death) and all-cause mortality at 6 months. Participants who reported persistent smoking and non-adherence to diet and exercise had a 3.8-fold increased risk of MI, stroke or death compared to never smokers who modified diet and exercise. It was not possible to determine the specific effects of diet and exercise on outcome.

In a study of the DASH diet plus lifestyle modification in 810 adults with above optimal blood pressure (Appel *et al.*, 2003), intervention resulted in significant reductions in systolic and diastolic blood pressure compared to lifestyle modification alone or controls. The effects of the intervention on mortality, cardiovascular events or stroke were not evaluated.

In conclusion, long-term adherence to cardioprotective diets, together with other lifestyle modifications such as smoking cessation, increased physical activity and reduced alcohol intake, may have a beneficial effect on stroke recurrence. Research is required to determine the specific effect of dietary modification on outcomes. The following evidence statements were developed:

B8.1 Commissioners should commission acute hospital health services to give all patients written information and advice on lifestyle changes that reduce the risk of stroke (RCP/ISWP, GRADE D).

B8.2 All patients who have had a stroke or transient ischaemic attack should receive advice on lifestyle factors that may modify lipid levels, including diet, physical activity, weight, alcohol and smoking (RCP/ISWP, GRADE A).

B8.3 All patients should be advised to eat the optimum diet:

Eating five or more portions of fruit and vegetables per day from a variety of sources.

Eating two portions of oily fish per week (salmon, trout, herring, pilchards, sardines, fresh tuna) (RCP/ISWP, GRADE A).

B9 In patients who have had a stroke, does the inclusion of individually tailored advice on modification of dietary risk factors (in multidisciplinary interventions) reduce stroke recurrence and mortality?

One Cochrane review (Brunner *et al.*, 2009) and one RCT (Ma *et al.*, 2009) were identified. The Cochrane review evaluating the effects of dietary advice on cardiovascular risk factors (Brunner *et al.*, 2009) concluded that dietary advice results in increased fruit and vegetable intakes and an increase in dietary fibre intake (and total and saturated fat intakes). Overall, the review concluded that dietary advice resulted in significant improvements in blood pressure, serum total and LDL cholesterol. Long-term studies evaluating the effects of interventions on stroke recurrence and mortality were not identified in this review. A randomised controlled trial in 419 patients to evaluate a nurse- and dietitian-led case-management programme for reducing major cardiovascular risk factors in low-income, primarily ethnic minority patients in the community (Ma *et al.*, 2009) resulted in a significantly lower Framingham risk score in the intervention group, mainly as a result of lowering blood pressure. In conclusion, although there is evidence that tailored dietary modifications result in improvements in cardiovascular risk factors, there is a lack of evidence for an effect of these interventions on stroke recurrence and mortality. The following evidence statements were developed:

B9.1 Commissioners should commission acute hospital health services to give all patients written information and advice on lifestyle changes that reduce the risk of stroke, tailored to the needs of the individual person (RCP/ISWP, GRADE D).

B9.2 Commissioners should facilitate the lifestyle recommendations made through supporting healthy eating (RCP/ISWP, GRADE D).

B9.3 Patients who are overweight or obese should be offered advice and support to aid weight loss, which may include diet, behavioural therapy and physical activity (RCP/ISWP, GRADE D).

Discussion

These guidelines provide evidence-based recommendations for use by healthcare professionals in the dietary components of lifestyle modification interventions for patients who have had a stroke. Evidence review reveals there is a lack of stroke-specific research in a number of key areas and highlights the need for large, good quality RCTs focusing on stroke recurrence.

Limitations

The present study summarises the recommendations as prepared for the 4th edition of the guidelines for which the final searches were run in October 2011 and have not been re-run subsequently. The authors of the present study acknowledge that any subsequent new papers published have not been cited in this manuscript. Without re-running the searches, the authors could not avoid publication bias with any certainty and therefore none of the known, more recent publications are included in the present work.

With reference to the recommendations around salt reduction (B1), subsequent to the guideline completion, two additional meta-analyses came to light (Hooper *et al.*, 2004; Taylor *et al.*, 2011). These were not detected in the systematic search of the literature because none of the designated search terms appeared in the abstracts// title/keywords.

Hooper *et al.* (2004) (Cochrane review) found that dietary interventions to reduce salt consumption produced only minimal effects on long term blood pressure. Taylor *et al.* (2011) (Cochrane review) found no strong evidence of benefit of dietary advice to reduce salt consumption in either cardiovascular morbidity or all-cause mortality. Because the guideline has already been published, it is not possible to include these findings; thus, the recommendation made under B1 above may be questioned. In the future, search terms will be re-discussed in accordance with RCP GDG to prevent similar omissions.The list of nutrients and diets was compiled using expert opinion and knowledge of the evidence base; however, it is not exclusive. Thus, it is possible that there may be studies evaluating other nutrients or non-nutrient dietary components that have not been identified in the present study.

Recommendations for clinical practice

The evidence reviewed as part of this guideline suggests that individually tailored dietary advice should be offered to patients who have had a stroke as part of a multidisciplinary lifestyle intervention designed to prevent stroke recurrence. Interventions should take into account each patient's specific risk factors (e.g. hypertension, hyperlipidaemia or diabetes mellitus) and should provide counselling and support of sufficient duration to result in long-term behaviour change.

Research recommendations

Although it might be predicted that diets associated with a decreased risk of having a stroke would be beneficial in terms of preventing stroke recurrence, there is still a lack of good quality studies investigating the effects of such diets in the secondary prevention of stroke.

There appears to be more evidence for prevention of cardiovascular events in those who have had MI or other cardiac diseases. This is an area that merits further research. Further studies are required to determine

whether the effects of dietary intervention and/or nutritional supplementation are synergistic with other lifestyle factors such as increased physical activity.

These guidelines include studies that use either dietary modification, dietary supplements in the form of capsules or a combination of both. It is yet to be determined whether the effects achieved by dietary modification can be achieved by dietary supplements and vice versa (i.e. does the individual nutrient or the mode of ingestion of the nutrient have the same effect on stroke recurrence?). It might be hypothesised that dietary supplementation with vitamins and minerals is only likely to be beneficial in the presence of deficiency. However, in the case of vitamin D, we found some evidence that, even in a deficient state, supplementation of vitamin D had no effect on stroke events (Elamin *et al.*, 2011), although this sub-analysis of two studies was likely underpowered. It should be noted that many of the studies included in these guidelines failed to determine nutrient status at baseline and/or at follow-up or provided supplementation in the presence of adequacy. Future studies should aim to take these considerations into account.

The role of other antioxidants in the secondary prevention of stroke (e.g. vitamins A and C or selenium) has yet to be determined and merits further research.

Several recent studies have shown a paradoxical association between body mass index (BMI) and mortality after stroke (Olsen *et al.*, 2008; Towfighi & Obviagele, 2009; Kim *et al.*, 2011, 2012; Ryu *et al.*, 2011; Vemmos *et al.*, 2011). This increased the mortality of underweight patients and the better survival of overweight and/or obese patients, as observed in both ischaemic and haemorrhagic strokes, suggests that weight management strategies targeting the optimal BMI range used for the healthy population may require further evaluation and individualisation in the secondary prevention of strokes. In the future, it would be important to evaluate other indicators of nutritional status and distribution of body fat, such as waist circumference, to scrutinise this paradox and its effect on stroke recurrence and mortality.

Finally, further research (both focused around primary and secondary prevention of stroke through nutrition or dietary means) should take into consideration the causes and risk factors for ischaemic and haemorrhagic strokes. Categorising both history of stroke and study outcomes (stroke events and stroke-related fatalities) according to these broad subtypes would further enhance the evidence base.

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CH identified search questions, helped to define the search terms, helped in review of abstracts, undertook quality review and led on the preparation of this manuscript. FG helped to define the search terms, conducted all literature searches, undertook some of the quality review and contributed to the preparation of the manuscript. CEW identified search questions, helped to define the search terms, reviewed all abstracts, undertook quality review and contributed to the preparation of this manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search terms used for the literature searches conducted in five electronic databases.

