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Plenary Lecture

B-vitamins and prevention of dementia

Robert Clarke
Clinical Trial Service Unit, Richard Doll Building, University of Oxford, Oxford OX3 7LF, UK

Elevated plasma homocysteine (Hcy) concentrations have been implicated with risk of cognitive impairment and dementia, but it is unclear whether low vitamin B_{12} or folate status is responsible for cognitive decline. Most studies reporting associations between cognitive function and Hcy or B-vitamins have used a cross-sectional or case–control design and have been unable to exclude the possibility that such associations are a result of the disease rather than being causal. The Hcy hypothesis of dementia has attracted considerable interest, as Hcy can be easily lowered by folic acid and vitamin B_{12}, raising the prospect that B-vitamin supplementation could lower the risk of dementia. While some trials assessing effects on cognitive function have used folic acid alone, vitamin B_{12} alone or a combination, few trials have included a sufficient number of participants to provide reliable evidence. An individual-patient-data meta-analysis of all randomised trials of the effects on cognitive function and vascular risk of lowering Hcy with B-vitamins will maximise the power to assess the epidemiologically-predicted differences in risk. Among the twelve large randomised Hcy-lowering trials for prevention of vascular disease, data should be available on about 30 000 participants with cognitive function. The principal investigators of such trials have agreed to combine individual-participant data from their trials after their separate publication.

Folate: Vitamin B_{12}: Homocysteine: Dementia

Elevated levels of serum total homocysteine (Hcy) have been linked with Alzheimer's disease and vascular dementia, but it is unclear whether this increase reflects underlying vascular disease that may have contributed to the dementia or insufficient folate or vitamin B_{12} status[1,2]. The Hcy hypothesis of dementia has attracted considerable interest because Hcy levels are easily lowered by dietary supplementation with folic acid and vitamin B_{12}[3], raising the prospect that these vitamins might prevent the onset of dementia. The initial epidemiological evidence in support of this hypothesis came from retrospective case–control studies that had reported that elevated plasma total Hcy levels were associated with Alzheimer's disease[1,4,5] or with cognitive impairment[6–15]. Recently, some prospective cohort studies[16,17], but not all[18], have also reported associations between dementia and elevated plasma total Hcy levels. Vitamin B_{12} deficiency is particularly common in older adults and the prevalence increases with age[19]. The introduction of mandatory folic acid fortification has prompted concerns about the safety for older adults with vitamin B_{12} deficiency, with some reports indicating that individuals with low vitamin B_{12} status have a more rapid deterioration in cognitive function in a setting of high intakes of folic acid[20–22].

The aims of the present review are to summarize: (1) current knowledge about the nutritional relevance of folate and vitamin B_{12}; (2) the importance of dementia for the population; (3) observational epidemiological associations between folate and vitamin B_{12} and dementia; (4) randomised trials of B-vitamins for the prevention of dementia.

Folate

Folate is a small water-soluble B-vitamin that is easily absorbed from the diet. Folate deficiency arises from poor diet, malabsorption or alcoholism, or from the use of certain drugs. It is common at all ages, including in

Abbreviations: Hcy, homocysteine; 5-MTHF, 5-methyltetrahydrofolate.
Corresponding author: Dr Robert Clarke, fax +44 1865 743985, email robert.clarke@ctsu.ox.ac.uk

childhood and during pregnancy. The prevalence of folate deficiency has declined markedly in populations with folate fortification. Folate is a cofactor for several different enzymes that enables them to transfer CH_3 groups required for the synthesis of DNA and proteins. Folate exists in different chemical forms distinguished by the oxidation state of the pteridine ring, the C_1 substitution at the N-5 and N-10 position and the number of conjugated glutamic acid residues attached to the molecule[23]. The attached groups differ according to the particular pathway to which the C group is going to be donated either as CH_3, formyl (-CHO) and methylene (-CH_2-), which are collectively termed 'one-carbon' (C_1) groups. The derivatives of folate present in the human body are chiefly reduced folates, tetrahydrofolates and dihydrofolate, whereas folic acid is the oxidised form. Folic acid is chemically stable and used as a nutritional supplement, alone or as a component of B-vitamin or multivitamin preparations and for fortification. Folic acid itself, however, is not biologically active, since it cannot bind and pass on C_1 groups. After entry into the small intestinal enterocyte, dihydrofolate reductase acts on folic acid to convert it, via dihydrofolate, to tetrahydrofolate. Subsequently, the tetrahydrofolate requires conversion to 5-methyltetrahydrofolate (5-MTHF) for it to enter the circulation in the same form as natural food folates. It has been shown that folic acid in doses >200–400 μg/d exceeds the potential for intestinal and hepatic reduction and methylation, causing unmetabolised folic acid to appear in the systemic circulation. 5-MTHF is the predominant form of circulating folate, and it is taken up by cells by a carrier protein and folate receptor. After cell entry 5-MTHF-monoglutamate is available for Hcy remethylation, catalysed by methionine synthase. Deficiency of vitamin B_{12} impairs the activity of methionine synthase and, as a result, 5-MTHF cannot donate its methyl group to Hcy, and Hcy levels rise. Since the conversion of methylenetetrahydrofolate to 5-MTHF is irreversible, there is no way back for 5-MTHF, and it becomes 'trapped' in its own metabolism. This 'folate trap' explains why vitamin B_{12} deficiency and folate deficiency share many features. The 'methylfolate trap' results in less recycling of folates to tetrahydrofolate, which eventually leads to impaired DNA synthesis (i.e. megaloblastic anaemia). High-dose folic acid supplementation may resolve the problem, since unmetabolised folic acid entering the cell can be reduced to tetrahydrofolate and can subsequently be used for DNA synthesis. Such folic acid will eventually also get trapped as 5-MTHF, but if it is supplied continuously it may reverse the DNA synthesis defect (i.e. correct the megaloblastic anaemia) without correcting the impaired methylation cycle[23].

Vitamin B_{12}

Vitamin B_{12} deficiency chiefly occurs in the elderly, in whom it is predominantly the result of malabsorption caused by lack of intrinsic factor (pernicious anaemia), gastric atrophy or ileal disease[24–27]. Age-independent causes include inadequate intake (e.g. vegetarians) or use of certain drugs. Severe folate and vitamin B_{12} deficiency often present with the identical haematological abnormality of macrocytic anaemia and megaloblastic bone marrow. Vitamin B_{12} deficiency also causes a demyelinating neurological disease, usually presenting as a peripheral neuropathy. The neurological symptoms of vitamin B_{12} deficiency may occur without anaemia, and early intervention is important in order to avoid irreversible damage. In man vitamin B_{12} serves as a cofactor in only two enzyme reactions: methionine synthase, which is responsible for the methylation of Hcy into methionine; methylmalonyl-CoA mutase, which transforms methylmalonyl-CoA into succinyl-CoA. Deficiency of vitamin B_{12} results in an accumulation of blood concentrations of Hcy and methylmalonic acid[24]. Low serum vitamin B_{12} concentrations have been reported in about 10% of older adults and the prevalence increases with age from about 5% at age 65 years to 20% at age 85 years[19,25]. In older adults individuals presenting with low vitamin B_{12} concentrations rarely have the classical features of macrocytic anaemia and neuropathy. More commonly, such individuals present with non-specific symptoms of fatigue and cognitive impairment that can be attributed to 'old age'. Some of the uncertainty about the importance of vitamin B_{12} deficiency relates to the limitations of the standard vitamin B_{12} assays. Low serum vitamin B_{12} concentrations do not accurately reflect intracellular vitamin B_{12} concentrations, and blood levels of Hcy or methylmalonic acid are believed to be more reliable indicators of intracellular vitamin B_{12} status. About 80% of vitamin B_{12} circulating in blood is biologically unavailable for most cells; the rest comprises holotranscobalamin, which is the part of serum vitamin B_{12} bound to transcobalamin, the protein that delivers the vitamin to cells in the body, and is easily measured[27].

The clinical symptoms of 'classical' vitamin B_{12} deficiency, i.e. severe megaloblastic anaemia combined with neuropsychiatric symptoms ('megaloblastic madness') are rarely seen today. Vitamin B_{12} deficiency is a slowly-progressive process that can take many years to develop. Nowadays, most cases are detected at an earlier stage, when clinical manifestations are often subtle and highly variable, and neuropsychiatric symptoms may occur in the absence of haematological signs. Thus, in clinical practice many patients may present with diffuse non-specific symptoms and vitamin B_{12} deficiency is only one of many differential diagnoses[26]. As a consequence, the diagnostic value of most of these symptoms and signs is low.

Homocysteine

Hcy is a S-containing amino acid derived from methionine (following the loss of a CH_3 group) that is present in all cells[23]. Hcy lies at a junction in C_1 metabolism between two metabolic cycles (remethylation and transulfuration) in all cells. In the remethylation pathway Hcy accepts a CH_3 group from 5-MTHF to form methionine. Vitamin B_{12} is a cofactor and 5-MTHF a substrate for this remethylation reaction that is catalysed by methionine synthase. In the transulfuration pathway Hcy condenses with serine to form cystathionine in an irreversible reaction catalysed by the

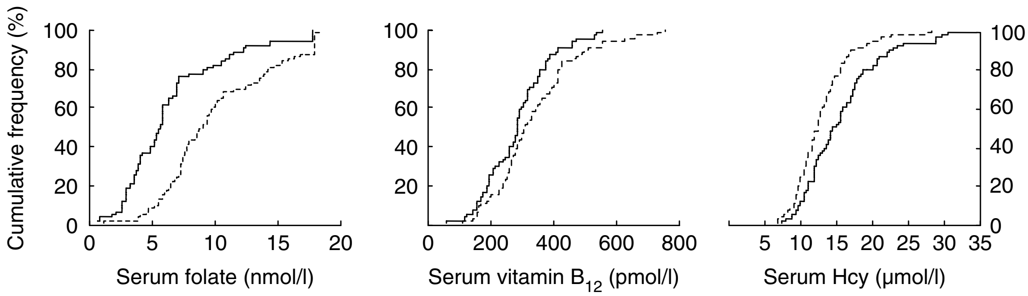

Fig. 1. Cumulative frequency of serum folate, vitamin B_{12} and homocysteine (Hcy) in patients with a histological diagnosis of Alzheimer's disease (—) and in controls (- -). (From Clarke *et al.*[1].)

vitamin B_6-dependent cystathionine β-synthase enzyme. The intracellular levels of Hcy are highly regulated and any increased production is met by export from cells. Consequently, plasma concentrations of Hcy reflect intracellular concentrations of Hcy and homeostasis of the enzymes involved in methionine metabolism to ensure a supply of CH_3 groups for essential reactions in all cells. Hence, elevated Hcy levels reflect both low levels of folate and of vitamin B_{12}.

Dementia

Dementia is characterised by an insidious slowly-progressive memory loss with alteration of higher intellectual function and cognitive abilities[28]. The term 'dementia' is used to describe a collection of symptoms, including a decline in memory, reasoning and communication skills, and a gradual loss of skills needed to carry out daily activities[28]. These symptoms are caused by structural and chemical changes in the brain as a result of physical diseases. Different types of dementia now distinguished include Alzheimer's disease, vascular dementia and dementia with Lewy bodies. Alzheimer's disease is the most common cause of dementia. Alzheimer's disease and vascular dementia have distinct pathological features, but these two disorders frequently co-exist and the combination is associated with a greater severity of cognitive impairment. While clinicians have placed much emphasis on the distinction between dementia and cognitive impairment, the distinction may be viewed as arbitrary. Cognitive impairment is a quantitative disorder and its distribution in the population shows a continuum of severity with dementia at the tail of the distribution. About one in five adults aged >80 years and one in twenty of those aged >65 years have some form of dementia. The fact that cognitive impairment is common in the population does not imply that it is intrinsic to ageing. The distribution of cognitive impairment is shifted downwards with increasing age, such that the mean scores decrease and the prevalence of cognitive impairment increases. The prevalence of dementia among individuals in institutions varies little by age or gender, increasing from about 55% among those aged 65–69 years to 65% in those aged ≥95 years. It has been estimated that 700 000 individuals have dementia in the UK or 1·1% of the entire UK population, of which about 62% have Alzheimer's disease and 27% have vascular dementia and mixed dementia. About two-thirds of individuals with late-onset dementia live in private households and one-third live in care homes. The proportion of those with dementia living in care homes rises steadily with age, from one-quarter of those aged 65–74 years to two-thirds of those aged ≥90 years.

While the aetiology of Alzheimer's disease is unknown, some experts have speculated that the accumulation of β-amyloid peptide in the brain is central to the pathogenesis of Alzheimer's disease[28]. Mutations in the amyloid precursor proteins that lead to pre-senile dementia and overexpression of β-amyloid protein in Down's syndrome and mouse knock-out models have provided support for this hypothesis. Alternative hypotheses for the aetiology of Alzheimer's disease have placed greater emphasis on the role of vascular factors and neuronal cell death. The onset of dementia is insidious and the underlying disease is believed to begin many years before the manifestation of symptoms of dementia.

Vitamin B_{12} and folate and risk of cognitive impairment and dementia

The hypothesis that elevated serum total Hcy may also be a risk factor for Alzheimer's disease was prompted by the observation in a retrospective case–control study that patients with histologically-confirmed Alzheimer's disease had higher concentrations of Hcy in blood samples collected before death than age-matched controls (Fig. 1)[1]. This longitudinal study compared Hcy levels taken during life from seventy-six cases with a histological diagnosis of 'Alzheimer's disease' made at post mortem with 108 controls without cognitive impairment. The results showed a 4·5 (95% CI 2·2, 9·2)-fold risk for histologically-confirmed Alzheimer's disease associated with Hcy levels in the upper, compared with the lower, third after controlling for age, gender, smoking, social class and apoE genotype. The Hcy measurements were carried out on blood samples that had been collected yearly for three successive years and were stable over this period and independent of the duration and severity of symptoms of dementia before enrolment.

Subsequently, several prospective studies have confirmed these findings[16,17] but some studies have been unable to confirm such associations[18]. The most reliable evidence for the relevance of Hcy to risk of dementia

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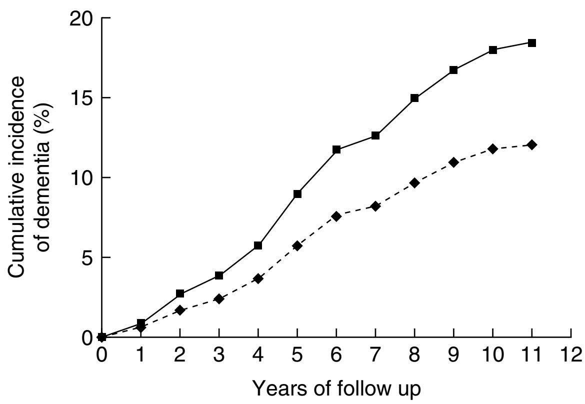

Fig. 2. Risk of dementia in relation to homocysteine concentrations. (■–■) Subjects in the highest quartile of plasma homocysteine at baseline; (◆- -◆), all other subjects. (From Seshadri *et al.*[16].)

comes from an 8-year follow-up prospective study of 1092 dementia-free elderly individuals that reported that elevated Hcy levels were associated with a 2-fold higher risk of dementia and of Alzheimer's disease (Fig. 2)[16]. After adjustment for age, gender, apo-E genotype and vascular risk factors excluding Hcy and plasma levels of folate and vitamins B_{12} and B_6, the relative risk for dementia was 1·4 (95% CI 1·1, 1·8) for a 1 SD increase in plasma Hcy concentrations[16].

Several prospective studies of individuals without dementia have reported an association between baseline Hcy and subsequent cognitive decline. For example, the MacArthur Study of Successful Aging involving 499 men aged 70–79 years has reported that elevated Hcy and low folate, vitamin B_{12} or vitamin B_6 status are each associated with poor cognitive function[12]. Brain-imaging studies have provided important information on the associations between Hcy and cognitive impairment and the underlying cerebrovascular and neurodegenerative changes. The initial case–control study of Hcy and Alzheimer's disease had shown that atrophy of the medial temporal lobe on computerised tomography scan of the brain of cases with Alzheimer's disease is more rapid in individuals with elevated Hcy concentrations[1]. In the Rotterdam Brain Scan Study of 1077 men and women aged 60–90 years plasma Hcy concentrations were found to be associated with increased risk of severe deep and periventricular white matter lesions and of silent brain infarcts in a cross-sectional analysis of MRI scans[29]. These MRI lesions were found to be three times more common in individuals in the top quintile of Hcy values compared with the bottom four quintiles. The severity of the white matter lesions was found to increase with increasing Hcy levels and the association remained significant even after adjustment for atherosclerotic disease and the presence of silent infarcts[29]. A subsequent analysis from the same study has reported that atrophy in the cerebral cortex and hippocampus is associated with elevated Hcy levels[30]. More recent evidence from a cross-sectional study of 1000 older adults in Banbury, Oxon., UK has demonstrated an association between cognitive impairment and low plasma levels of holotranscobalamin (the active fraction of vitamin B_{12}) and with high levels of methylmalonic acid (a metabolic marker of vitamin B_{12} deficiency) in addition to elevated Hcy concentrations[26].

It is possible that low vitamin B_{12} may have an effect on risk of dementia that is independent of differences in plasma Hcy. Many of the Hcy-lowering trials designed for the prevention of CHD and stroke will include some assessment of cognitive function and may provide evidence about whether lowering Hcy concentrations (and administration of high-dose vitamin B_{12}) could slow the rate of cognitive decline.

Possible hazards of folic acid

Concerns that folic acid fortification could delay the diagnosis of vitamin B_{12} deficiency or exacerbate the neurological or neuropsychiatric complications of vitamin B_{12} deficiency has delayed the introduction of folic acid fortification in the UK[31]. Both case studies and epidemiological studies have reported that excessive intakes of folic acid among older adults with vitamin B_{12} deficiency are associated with a more rapid progression of neuropathy or cognitive impairment[20,21,32–34]. About 10–25% of older adults have biochemical evidence of low vitamin B_{12} status, defined by a low serum concentration (<45 pmol/l) of holotranscobalamin, which is a more sensitive test of vitamin B_{12} deficiency than conventional vitamin B_{12} testing[27]. There have been reports that patients with pernicious anaemia who are treated with folic acid have an accelerated decline in neurological function[32–34]. Consequently, the amount of folic acid is routinely limited to a maximum of 1000 μg/d because of concerns about the adverse effects of high-dose folic acid in individuals with vitamin B_{12} deficiency. In 1998 the USA introduced mandatory folic acid fortification of all grain products at a dose of 140 μg/100 g grain. It was believed that this level of fortification would increase the average daily intake by 100 μg/d. The prevalence of low serum folate has decreased from 16–22% pre-fortification to 0·5–1·7% post-fortification[35]. The required level of fortification was considered generally safe. However, concern persists about the safety of folic acid fortification in older adults with vitamin B_{12} deficiency. In the USA the introduction of folic acid fortification has resulted in 200–300% increases in serum folate concentrations[35] and voluntary fortification in the UK has resulted in substantial changes in serum folate concentrations[31].

Elevated Hcy levels in older adults may reflect impaired status of vitamin B_{12}, folate or a combination. However, the relative importance of vitamin B_{12} deficiency as a determinant of Hcy concentrations and cognitive impairment is probably greater than that of folate deficiency in older adults[27]. Cross-sectional studies of older adults have shown that a high proportion of older adults have biochemical evidence of low vitamin B_{12} status, and the prevalence of low vitamin B_{12} status increases from 5% at age 65 years to 20% at age 80 years[25]. The extent to which the associations between low vitamin B_{12} status and risk of dementia are causal is unclear[1,2]. Moreover, low vitamin B_{12} status may be more relevant in the setting of

Table 1. Characteristics of the homocysteine-lowering trials for prevention of CVD

Trial	Country	Previous disease	No. of subjects randomised (planned or actual)	Scheduled duration of treatment (years)	Folic acid (mg)	Vitamin B_{12} (mg)	Vitamin B_6 (mg)	Observed or estimated difference in plasma homocysteine (%)
CHAOS-2*	UK	CHD	1882	2	5·0	–	–	13
SU.FOL.OM3†	France	CHD	1862	5	0·5	0·02	3	25
WENBIT‡	Norway	CHD	3096	3	0·8	0·4	40	25
NORVIT	Norway	CHD	3749	3	0·8	0·4	40	25
SEARCH§	UK	CHD	12064	7	2·0	1·0	–	25
HOPE-2‖	Canada	CHD	5522	5	2·5	1·0	50	20
WACS¶	USA	CHD	5442	7·4	2·5	1·0	50	20
SU.FOL.OM3†	France	Stroke	640	5	0·5	0·02	3	25
VITATOPS**	Australia	Stroke	(8000)	3	2·0	0·5	25	25
VISP††	USA	Stroke	3680	2	2·5	0·4	25	15
FAVORIT‡‡	USA	Renal	4111	7	2·5	1·0	50	33
HOST§§	USA	Renal	2056	5	40·0	2·0	100	33

CHAOS-2, Second Cambridge Anti-Oxidant Heart Study; SU.FOL.OM3, Supplementation en Folate et Omega-3; WENBIT, West of Norway Vitamin Intervention Trial; NORVIT, Norwegian Vitamin Intervention Trial; SEARCH, Study of Additional Reductions in Cholesterol and Homocysteine; VISP, Vitamin Intervention for Stroke Prevention; HOPE-2, Heart Outcomes Prevention Evaluation-2; WACS, Women's Antioxidant Cardiovascular Study; VITATOPS, The Vitamin Intervention to Prevent Strokes Trial; FAVORIT, Folic Acid for Vascular Outcome Reduction In Transplantation; HOST, Homocysteine Study Veteran Affairs Cooperative Study.

*Trial terminated early after a median duration of treatment of 1·7 years; 187 participants experienced a vascular event.

†Trial scheduled to be completed in 2009.

‡Trial terminated early after the publication of the null findings of NORVIT; results scheduled to be published in 2007.

§Trial scheduled to be completed in 2008.

‖Trial was carried out mainly in Canada and USA (both populations with mandatory folic acid fortification), but also included some participants from Brazil, Slovakia and Western Europe.

¶Trial treatment completed; results scheduled to be published in 2007.

**Participants recruited from twenty countries (Australia, Belgium, Brazil, Hong Kong, India, Italy, Malaysia, Moldova, Netherlands, New Zealand, Pakistan, Philippines, Portugal, Republic of Georgia, Serbia, Monte Negro, Singapore, Sri Lanka, UK and USA) and scheduled to be completed in 2008.

††The trial terminated early; no significant effect on the risk of recurrent stroke during the 2 years of follow-up.

‡‡Trial scheduled to be completed in 2011.

§§Scheduled trial treatment period now completed; results scheduled to be published in 2007.

mandatory folic acid fortification. Consequently, there is some concern, particularly in countries with mandatory folic acid fortification, that individuals with low vitamin B_{12} status may have more rapid deterioration of neurological function in the context of a high intake of folate. A recent cross-sectional study of 1459 older adults in the USA carried out after the introduction of mandatory fortification has reported that low vitamin B_{12} (<150 pmol/l) and high serum folate (>60 nmol/l) is associated with a 5-fold increased risk of cognitive impairment[21] compared with with normal levels, providing some evidence of a possible hazard of high levels of folic acid fortification.

It is important to ascertain the relevance, if any, of vitamin B_{12} for risk of brain disease in older adults by carrying out randomised trials of vitamin B_{12} supplements in older adults. Table 1 shows several completed and ongoing randomised trials that have assessed, or are assessing, the effects of Hcy-lowering vitamin supplements on vascular disease[2,36]. It is unclear whether any of these trials will be able to determine the independent relevance of vitamin B_{12} to folic acid use for prevention of cognitive impairment (Table 2).

Cumulative meta-analysis of all randomised trials will assess the effects of lowering Hcy levels with B-vitamins on risk of CVD[36]. An individual-patient-data meta-analysis of all randomised trials of the effects on vascular risk of lowering Hcy with B-vitamins will maximise the power to assess the epidemiologically-predicted differences in risk (Table 2). Among the twelve randomised Hcy-lowering trials for prevention of CVD involving >1000 participants, data should be available on about 52 000 participants (32 000 with previous CVD in unfortified populations; 14 000 with previous CVD and 6000 with renal disease in fortified populations). In order to minimise bias the design and primary analyses to be carried out have been pre-specified. The analyses will include assessment of effects on major vascular events, stroke and major coronary events, in addition to venous thrombosis, cancer and cognitive function. Additional analyses will assess effects on vascular outcomes in subgroups defined by population, previous disease, the per 3 μmol/l difference in Hcy levels achieved by treatment, pre-treatment vitamin status, duration, age, gender and vascular events excluding revascularisations and, separately, excluding vascular events occurring during the first year of treatment. This meta-analysis of the Hcy-lowering trials should ensure that reliable evidence emerges about the effects of lowering Hcy on risk of vascular and non-vascular outcomes, including cognitive function.

Further trials of vitamin B_{12} supplementation or placebo involving a large number of elderly participants who are high risk are required in order to assess the relevance of vitamin B_{12} supplements or placebo for the prevention of cognitive impairment and dementia. In the Folic Acid and Carotid Intima-media Thickness Trial 818 healthy middle-aged adults (age 60 years) were randomised to folic acid (0·8 mg) for 3 years, resulting in a 26 % lowering of Hcy concentration and a modest improvement in some domains

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Table 2. Estimated power of the individual homocysteine-lowering trials and combination of the large trials in individuals with previous CHD, stroke or renal disease to detect differences in risk of 10% or 20% for major coronary events (MCE; non-fatal MI + fatal CHD), stroke (non-fatal or fatal stroke) and major vascular events (MVE; non-fatal MI + fatal CHD + non-fatal stroke + revascularisation)*

		Estimated no. of events			10% reduction in risk; approx power at $2P<0.05$			20% reduction in risk; approx power at $2P<0.05$		
Population or trial	n†	MCE	Stroke	MVE	MCE	Stroke	MVE	MCE	Stroke	MVE
CHD										
CHAOS-2	1882	87	32	226	5	4	7	9	6	17
SU.FOL.OM3	1862	190	190	626	12	12	36	36	36	92
WENBIT	3096	284	77	950	12	7	28	38	17	83
NORVIT	3749	606	94	1575	29	7	79	85	19	99
SEARCH	12064	1400	373	2800	55	18	89	99	59	99
HOPE-2	5522	718	276	1795	22	11	58	70	32	99
WACS	5442	140	148	796	10	7	26	31	17	79
All CHD	33755	3425	1185	8768	86	39	99	99	94	99
Stroke										
SU.FOL.OM3	640	95	95	358	8	8	24	21	21	75
VITATOPS	8000	321	951	1690	16	41	68	53	95	99
VISP	3680	221	288	504	7	8	11	16	20	34
All stroke	12680	637	1334	2552	21	46	78	69	97	99
Renal										
FAVORIT	4111	480	220	1000	37	18	72	94	63	99
HOST	2056	247	113	514	21	12	45	71	37	97
All renal	6056	727	333	1514	52	26	88	99	80	99

CHAOS-2, Second Cambridge Anti-Oxidant Heart Study; SU.FOL.OM3, Supplementation en Folate et Omega-3; WENBIT, West of Norway Vitamin Intervention Trial; NORVIT, Norwegian Vitamin Intervention Trial; SEARCH, Study of Additional Reductions in Cholesterol and Homocysteine; VISP, Vitamin Intervention for Stroke Prevention; HOPE-2, Heart Outcomes Prevention Evaluation-2; WACS, Women's Antioxidant Cardiovascular Study; VITATOPS, The Vitamin Intervention to Prevent Strokes Trial; FAVORIT, Folic Acid for Vascular Outcome Reduction In Transplantation; HOST, Homocysteine Study Veteran Affairs Cooperative Study; approx, approximate.

*For details of trials, see Table 1.

†No. of subjects scheduled to be randomised.

of cognitive function[37]. A systematic review of fourteen randomised trials of vitamin B_6, vitamin B_{12} or folic acid supplementation and cognitive function has concluded that there is insufficient evidence of beneficial effects of these vitamins on cognitive function[38].

The results of these ongoing trials of B-vitamins are required before B-vitamin supplementation can be recommended for the prevention of dementia[35]. Nevertheless, the available evidence suggests that the benefits of folic acid fortification for the prevention of neural-tube defects are likely to outweigh any possible hazards of folic acid fortification for older adults provided public health strategies avoid an excessive intake of folic acid in older adults with vitamin B_{12} deficiency. Thus, if mandatory fortification with folic acid is introduced in the UK it will be important to control voluntary fortification of breakfast cereals and spreads (which have already had a substantial effect on increasing the population mean folate levels) to avoid any potential hazard in older adults associated with excessive intakes of folic acid in the setting of vitamin B_{12} deficiency.

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