Elevated plasma homocysteine (Hcy) concentrations have been implicated with risk of cognitive impairment and dementia, but it is unclear whether low vitamin B\textsubscript{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\textsubscript{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\textsubscript{12} alone or a combination, few trials have included a sufficient number of participants to provide reliable evidence. An individual-participant-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\textsubscript{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\textsubscript{12} status\textsuperscript{(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\textsubscript{12}\textsuperscript{(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\textsuperscript{(1,4,5)} or with cognitive impairment\textsuperscript{(6–15)}. Recently, some prospective cohort studies\textsuperscript{(16,17)}, but not all\textsuperscript{(18)}, have also reported associations between dementia and elevated plasma total Hcy levels. Vitamin B\textsubscript{12} deficiency is particularly common in older adults and the prevalence increases with age\textsuperscript{(19)}. The introduction of mandatory folic acid fortification has prompted concerns about the safety for older adults with vitamin B\textsubscript{12} deficiency, with some reports indicating that individuals with low vitamin B\textsubscript{12} status have a more rapid deterioration in cognitive function in a setting of high intakes of folic acid\textsuperscript{(20–22)}.

The aims of the present review are to summarize: (1) current knowledge about the nutritional relevance of folate and vitamin B\textsubscript{12}; (2) the importance of dementia for the population; (3) observational epidemiological associations between folate and vitamin B\textsubscript{12} and dementia; (4) randomised trials of B-vitamins for the prevention of dementia.
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 CH₃ 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 C₁ 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 CH₃, formyl (-CHO) and methylene (-CH₂-), which are collectively termed ‘one-carbon’ (C₁) 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 C₁ 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 B₁₂ 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 B₁₂ 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 B₁₂**

Vitamin B₁₂ deficiency chiefly occurs in the elderly, in whom it is predominantly the result of malabsorption caused by lack of intrinsic factor (pernicious anaemia), gastriac atrophy or ileal disease(24–27). Age-independent causes include inadequate intake (e.g. vegetarians) or use of certain drugs. Severe folate and vitamin B₁₂ deficiency often present with the identical haematological abnormality of macrocytic anaemia and megaloblastic bone marrow. Vitamin B₁₂ deficiency also causes a demyelinating neurological disease, usually presenting as a peripheral neuropathy. The neurological symptoms of vitamin B₁₂ deficiency may occur without anaemia, and early intervention is important in order to avoid irreversible damage. In man vitamin B₁₂ 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 B₁₂ results in an accumulation of blood concentrations of Hcy and methylmalonic acid(24). Low serum vitamin B₁₂ 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 B₁₂ 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 B₁₂ deficiency relates to the limitations of the standard vitamin B₁₂ assays. Low serum vitamin B₁₂ concentrations do not accurately reflect intracellular vitamin B₁₂ concentrations, and blood levels of Hcy or methylmalonic acid are believed to be more reliable indicators of intracellular vitamin B₁₂ status. About 80% of vitamin B₁₂ circulating in blood is biologically unavailable for most cells; the rest comprises holotranscobalamin, which is the part of serum vitamin B₁₂ 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 B₁₂ deficiency, i.e. severe megaloblastic anaemia combined with neuropsychiatric symptoms (‘megaloblastic madness’) are rarely seen today. Vitamin B₁₂ 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 B₁₂ 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 CH₃ group) that is present in all cells(21). Hcy lies at a junction in C₁ metabolism between two metabolic cycles (remethylation and transulfuration) in all cells. In the remethylation pathway Hcy accepts a CH₃ group from 5-MTHF to form methionine. Vitamin B₁₂ 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
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.

**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.

**Vitamin B12 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
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)\(^\text{16}\). 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\(^\text{16}\).

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\(^\text{12}\). 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\(^\text{1}\). 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\(^\text{29}\). 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\(^\text{29}\). A subsequent analysis from the same study has reported that atrophy in the cerebral cortex and hippocampus is associated with elevated Hcy levels\(^\text{30}\). 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\(^\text{26}\).

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 have delayed the introduction of folic acid fortification in the UK\(^\text{31}\). 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\(^\text{27}\). 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 \(\mu\)g/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 \(\mu\)g/100 g grain. It was believed that this level of fortification would increase the average daily intake by 100 \(\mu\)g/d. The prevalence of low serum folate has decreased from 16–22% pre-fortification to 0.5–1.7% post-fortification\(^\text{35}\). 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\(^\text{35}\) and voluntary fortification in the UK has resulted in substantial changes in serum folate concentrations\(^\text{31}\).

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\(^\text{27}\). 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\(^\text{25}\). The extent to which the associations between low vitamin B\(_{12}\) status and risk of dementia are causal is unclear\(^\text{1,12}\). Moreover, low vitamin B\(_{12}\) status may be more relevant in the setting of
null findings of NORVIT; results scheduled to be published in 2007.
†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 terminated early after the publication of the null findings of NORVIT; results scheduled to be published in 2007.
‡‡Participants recruited from twenty countries (Australia, Belgium, Brazil, Hong Kong, Italy, India, Malaysia, Moldova, Netherlands, New Zealand, Pakistan, Philippines, Portugal, Republic of Georgia, Serbia, Montenegro, Singapore, Sri Lanka, UK and USA) and scheduled to be completed in 2008.
†††Trial terminated early; no significant effect on the risk of recurrent stroke during the 2 years of follow-up.
§§Switched trial treatment period now completed; results scheduled to be published in 2007.

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 B12 supplementation or placebo involving a large number of elderly participants who are high risk are required in order to assess the relevance of vitamin B12 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.
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.

### 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 + non-fatal stroke + revascularisation)*

<table>
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<tr>
<th>Population or trial</th>
<th>Estimated no. of subjects scheduled to be randomised</th>
<th>MCE</th>
<th>Stroke</th>
<th>MVE</th>
<th>10% reduction in risk; approx power at 2P&lt;0.05</th>
<th>MCE</th>
<th>Stroke</th>
<th>MVE</th>
<th>20% reduction in risk; approx power at 2P&lt;0.05</th>
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<td>74</td>
<td>950</td>
<td>12</td>
<td>7</td>
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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.

### References


