REVIEW ARTICLE

Vitamin B_6, B_{12}, and Folic Acid Supplementation and Cognitive Function

A Systematic Review of Randomized Trials

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Background: Despite their important role in cognitive function, the value of B vitamin supplementation is unknown. A systematic review of the effect of pyridoxine hydrochloride (hereinafter "vitamin B_6"), cyanocobalamin or hydroxycobalamin (hereinafter "vitamin B_{12}"), and folic acid supplementation on cognitive function was performed.

Methods: Literature search conducted in MEDLINE with supplemental articles from reviews and domain experts. We included English language randomized controlled trials of vitamins B_6 and/or B_{12} and/or folic acid supplementation with cognitive function outcomes.

Results: Fourteen trials met our criteria; most were of low quality and limited applicability. Approximately 50 different cognitive function tests were assessed. Three trials of vitamin B_6 and 6 of vitamin B_{12} found no effect overall in a variety of doses, routes of administration, and populations. One of 3 trials of folic acid found a benefit in cognitive function in people with cognitive impairment and low baseline serum folate levels. Six trials of combinations of the B vitamins all concluded that the interventions had no effect on cognitive function. Among 3 trials, those in the placebo arm had greater improvements in a small number of cognitive tests than participants receiving either folic acid or combination B-vitamin supplements. The evidence was limited by a sparsity of studies, small sample size, heterogeneity in outcomes, and a lack of studies that evaluated symptoms or clinical outcomes.

Conclusion: The evidence does not yet provide adequate evidence of an effect of vitamin B_6 or B_{12} or folic acid supplementation, alone or in combination, on cognitive function testing in people with either normal or impaired cognitive function.

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GLOBALLY, 24 MILLION people have some form of dementia, with 4.6 million new cases diagnosed each year.[1] It is estimated that the number of people affected will double every 20 years and reach 81 million by 2040. Pharmacotherapy of Alzheimer disease and other dementias can provide only modest cognitive or disease-modifying benefits.[2] However, even modest benefits may have significant effects on quality of life, caregiver burden, and societal economic costs. Increased homocysteine levels in conjunction with low levels of folate, vitamin B_6, and vitamin B_{12}, which interact to control homocysteine, have been reported to correlate with decreased performance on cognitive tests.[3-5] For these reasons, B vitamin supplementation has been proposed to prevent or reverse cognitive decline.

This systematic review examines whether supplementation with pyridoxine hydrochloride (hereinafter "vitamin B_6"), cyanocobalamin or hydroxycobalamin (hereinafter "vitamin B_{12}"), and folic acid can prevent, decrease the progression rate of, or reverse the neurologic changes associated with age-related neurodegenerative conditions such as Alzheimer disease in humans. The review was conducted as part of a larger evidence report on the association between B vitamins and berries and neurocognitive function.[6]

METHODS

STUDY ELIGIBILITY

We conducted a comprehensive literature search for publications on B vitamins in MEDLINE and Commonwealth Agricultural Bureau (CAB) Abstracts from inception through

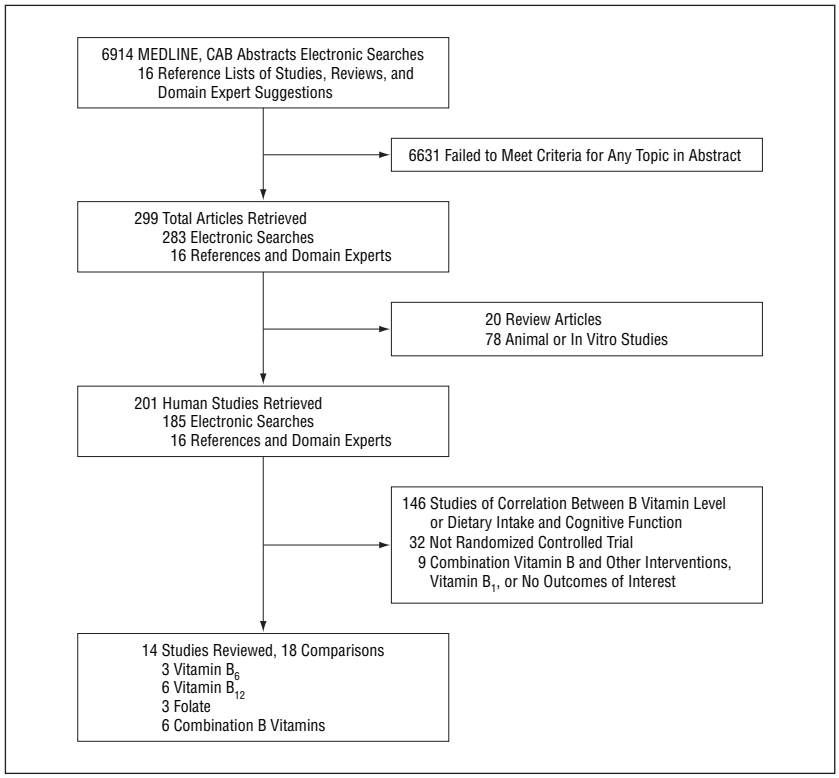

Figure. Flow diagram of study selection process. CAB indicates Commonwealth Agricultural Bureau.

February 2, 2005; an update limited to randomized trials and systematic reviews was performed on August 17, 2006. Search terms included the common and chemical names for the B vitamins (*folic acid*, *folate*, *pteroylglutamic*, *folacin*, *riboflavin*, *lactoflavin*, *thiamin(e)*, *cobalamin*, *cyanocobalamin*, *pyridoxine*, *pyridoxal*, *pyridoxamine*, and *vitamins* B_1, B_2, B_6, and B_{12}) and neurocognitive terms including *nervous system diseases*, *cognitive disorders*, *delirium*, *amnestic*, *neurodegeneration*, *dementia*, *Alzheimer*, *Lewy body*, *brain*, *neuron*, and *nerve cell*. Additional studies were sought from neurology and vitamin research experts and from reference lists of selected articles, review articles, and meta-analyses.

Study eligibility criteria included peer-reviewed reports of randomized controlled trials of clearly defined B vitamin supplements (B_6, B_{12}, and folic acid), where specific type of vitamin, dose, and route of administration were reported. We included English language publications of trials of adult participants with outcomes related to diagnosis or severity (degree) of Alzheimer disease, other age-related neurocognitive disorders, cognitive impairment, or tests of cognitive function. We excluded studies of mental retardation, encephalopathies, peripheral neuropathy and other lower motor neurodegeneration, subacute combined degeneration, vascular dementia, and mixed causes of dementia lacking separate analyses for disease types. We also excluded studies of "multivitamins" that included vitamins other than B vitamins.

STUDY SELECTION AND DATA EXTRACTION

All citations identified through the literature search were screened according to the eligibility criteria, and retrieved articles were evaluated against the same criteria. Each accepted study was extracted by a single reviewer, and a second reviewer independently verified the extracted data. Data extraction issues were resolved by consensus.

METHODOLOGIC QUALITY GRADE

We used a 3-category grading system to denote the methodologic quality of each trial[6,7]: (1) *Good quality* studies had the least bias. These studies mostly adhered to the commonly held concepts of good quality: they were formal and randomized with a clear description of the population, setting, interventions, and comparison groups; they used appropriate outcome measurements, statistical and analytic methods, and reporting conventions; and they contained no reporting errors, less than a 20% dropout rate, clear reporting of dropouts, and no obvious bias. (2) *Fair quality* studies were susceptible to some bias. They had some deficiencies but none likely to cause major bias. (3) *Poor quality* studies had significant bias. They had serious errors in design, analysis, or reporting or may have had a large amount of missing information or discrepancies in reporting. Each included study was graded by at least 2 people. When there were disagreements, additional reviewers graded the studies, and consensus was reached.

APPLICABILITY GRADE

Applicability addresses the relevance of a given study that is distinct from the question of the study's methodologic quality. The applicability of a study is dictated by the questions and populations that are of interest to those analyzing the studies.

We categorized studies within a target population into 1 of 3 levels of applicability[6,7]: (1) In *widely applicable* studies, the sample was representative of individuals at increased risk for, or diagnosed as having, age-related neurocognitive disorders. They included both sexes, an appropriate age range, and other important features of the target population (eg, general health status). At least 30 participants were analyzed. (2) For *moderately applicable* studies, the sample was representative of a relevant subgroup of the target population but not the entire population. Limitations included such factors as a narrow age range and a setting that applied to only a portion of the general population (eg, nursing home). At least 10 participants were analyzed. (3) In *narrowly applicable* studies, the sample was representative of a narrow subgroup of participants only and was of limited applicability to other subgroups.

On review of the literature, we determined that studies of short-term B vitamin supplementation (ie, 1 or 3 months), but longer-term cognitive testing (ie, at 3 or 12 months), were of lesser relevance to the question of whether B vitamin supplementation should be recommended to prevent cognitive decline. These studies were included but deemed to be of limited applicability.

OUTCOMES AND METRICS REPORTED

We evaluated all outcomes relevant to neurocognitive function that were reported in studies. In all included trials, this involved the use of one or more cognitive function tests or subtests.

Three sets of data were evaluated: (1) the mean baseline levels in both intervention and control arms, (2) within-

Table 1. Summary of Intervention Studies Evaluating the Effect of B Vitamins on Neurocognitive Outcomes

Vitamin Supplementation	Studies, No.	Participants, No.*	Quality, No.			Applicability, No.			Results
			Good	Fair	Poor	Wide	Moderate	Narrow	
B_6	3	145	1	1	1	0	1	2	No association
B_{12}	6	210	1	3	2	0	2	4	No association or worse outcome†
Folic acid	3	39	0	2	1	0	1	2	No association or improved outcome‡
Combination B_6, B_{12}, and folic acid	6	472	2	2	2	2	2	2	No association or worse outcome§

Abbreviations: Vitamin B_6, pyridoxine hydrochloride; vitamin B_{12}, cyanocobalamin or hydroxycobalamin.
*Receiving B vitamin supplementation. For vitamins B_6, B_{12}, and folic acid, these numbers are approximate because Bryan et al[9] reported only that 75 participants were randomized to 1 of the B vitamins or placebo. For combination treatment, the number is approximate because Clarke et al[18] reported only that 128 participants with data on cognitive function were randomized between B vitamins and placebo.
†Statistically significant net worsening in cognitive function reported in a small minority of cognitive tests performed.
‡One study found a benefit in people with cognitive impairment and low baseline serum folate levels.
§Two studies found greater improvement in several cognitive function tests among people with normal cognitive function in the placebo group than among those in the combination B vitamin group.

Table 2. Effect of Pyridoxine Hydrochloride (Vitamin B_6) Intervention on Cognitive Function Tests

Source	Dose, mg/d (Duration)	B Vitamin Participants (Controls), No.	Population Characteristic (Mean Age, y)	Quality/ Applicability	Test	Maximum Score*	Intervention (Control) Base Value	Intervention (Control) Change		Net Change	
								Value	*P* Value	Value	*P* Value
Stott et al,[8] 2005	25 (3/12 mo†)	88/78‡ (78)	Ischemic vascular disease (74)	Good/narrow	Telephone interview for cognitive status[20]	39	25.5 (ND)	−0.2 (0.0)	NS (NS)	−0.2	NS
					Letter-digit coding test[21]	ND	19.7 (ND)	−0.6 (0.0)	NS (NS)	−0.6	NS
Bryan et al,[9] 2002	75 (5 wk)	~19 (~19)§	Normal (74)	Fair/narrow	Digit-symbol coding (WAIS)[22]	ND	63.4 (62.3)	+7.3 (+4.8)	NS (NS)	+2.5	NS
					Verbal ability–vocabulary (WAIS)[22]	ND	22.1 (21.9)	+0.6 (−0.2)	NS (NS)	+0.8	NS
					Digit span–backward (WAIS)[22]	ND	6.1 (7.1)	0.0 (+0.4)	NS (NS)	−0.4	NS
					Stroop[23]	ND	2.34 (2.51)	−0.06 (−0.12)	NS (NS)	+0.06	NS
					Verbal fluency–initial letter[24]	ND	29.3 (23.7)	+1.2 (+3.3)	NS (NS)	−2.1	NS
Deijen et al,[10] 1992	12 (12 wk)	38 (38)	Normal (83)	Poor/moderate	Associate recognition task[25]	9	3.2‖ (3.9‖)	+0.1 (−1.1)	NS (ND)	+1.2	ND
					Long-term memory storage[25]	9¶	0.35 (0.45)	−0.35 (+0.45)	ND (ND)	−0.8¶	<.03

Abbreviations: ND, no data; NS, nonsignificant; Stroop, Stroop Color-Word Test; vitamin B_6, pyridoxine hydrochloride; WAIS, Wechsler Adult Intelligence Scale.
*Unless otherwise indicated, higher score indicates better cognitive function.
†Intervention lasted 12 weeks; follow-up cognitive testing occurred at 1 year.
‡Number tested with telephone interview of cognitive status[20]/number tested with letter digit coding test.[21]
§Seventy-five participants were randomized among vitamins B_6, B_{12}, folic acid, and placebo.
‖Results reported graphically.
¶Lower score indicates better cognitive function.

cohort changes (ie, final minus baseline values), and (3) the net change of the outcome (change in intervention cohort minus control cohort). In addition, we included the reported *P* values of both the within-cohort change and the net change. We reported *P* value less than .10; those above .10 and those reported as nonsignificant were described as "NS."

RESULTS

The literature searches yielded 6914 citations, of which 185 articles were retrieved. An additional 16 studies were identified in review articles and study reference lists or were forwarded by domain experts. From these 202 articles, 14 randomized controlled trials of vitamins B_6, B_{12}, and folic acid supplementation qualified for this review (these included 18 comparisons of B vitamins with placebo).[8-19] Among the rejected studies, 146 were studies of correlations between B vitamin levels or dietary intake and cognitive function; 32 were other nonrandomized studies; and 9 randomized trials did not evaluate either interventions or outcomes of interest (**Figure**). One trial reported separate data for different age groups of cognitively normal women.[9] After reviewing all studies, we included only the data from the older cohort of women, aged 65 to 92 years, to be consistent with the other trials, which all included only older participants. **Table 1** lists the number

Table 3. Effect of Cyanocobalamin or Hydroxycobalamin (Vitamin B_{12}) Intervention on Cognitive Function Tests in Randomized Controlled Trials

Source	Dose (Duration)	B Vitamin Participants (Controls), No.	Population Characteristic (Mean Age, y)	Quality/ Applicability	Test	Maximum Score*	Intervention (Control) Base Value	Intervention (Control) Change		Net Change	
								Value	*P* Value	Value	*P* Value
Hvas et al,[11] 2004	1 mg/wk, injection (1/3 mo†)	70 (70)	Cognitive impairment (75)	Good/narrow	MMSE[26]	30	26 (27)	+0.3 (+0.2)	NS (NS)	+0.1	NS
					CAMCOG[27]	100	89 (89)	+1.3 (+1.9)	.04 (.001)	–0.6	NS
					12-Word learning test–immediate[28]	12	5 (5)	+0.2 (+0.4)	NS (.04)	–0.2	NS
					12-Word learning test–15 minutes[28]	12	2 (2)	+0.2 (+0.7)	NS (.001)	–0.5	.04‡
Eussen et al,[29] 2006	1 mg/d, oral (24 wk)	64 (65)	Normal to cognitive impairment (73)	Fair/moderate	Digit span–forward (WAIS)[22]	16	7.4 (7.6)	+0.1 (+0.2)	NS (NS)	–0.1	NS
					Digit span–backward (WAIS)[22]	14	4.9 (4.7)	–0.3 (+0.6)	<.05 (<.05)	–0.9	.001‡
					Executive function similarities (WAIS)[30]	12	5.3 (4.8)	+0.8 (+0.6)	NS (NS)	+0.2	NS
					Speed–finger tapping, ms[31]	ND§	453 (409)	–41 (–20)	NS (NS)	–21	NS
					Speed–trail-making test, part A[32]	ND§	75.4 (72.0)	+2.1 (+1.9)	NS (NS)	+0.2	NS
					15-Word learning–immediate recall[33]	75	30.9 (30.0)	+4.3 (+5.7)	NS (NS)	–1.4	NS
					15-Word learning–delayed recall[33]	15	4.8 (5.1)	+0.7 (+1.0)	NS (NS)	–0.3	NS
					15-Word learning–recognition[33]	30	25.9 (25.3)	+0.7 (+1.7)	<.05 (<.05)	–1.0	.03‡
					Executive function–trail-making test, part C/part A,[32]	ND§	2.7 (2.9)	+0.1 (–0.1)	NS (NS)	+0.2	NS
					Executive function–Stroop test, part 3/part 2[34]	ND§	2.2 (2.1)	0.0 (+0.7)	NS (NS)	–0.7	NS
					Construction–complex figure of Rey, copy[35]	36	28.0 (27.7)	+2.0 (+1.5)	NS (NS)	+0.5	NS
					Speed–motor planning 2, ms[31]	ND§	627 (673)	+20 (–55)	NS (NS)	+75	NS
					Executive function–motor planning 3, ms[31]	ND§	898 (1012)	–35 (–22)	NS (NS)	–13	NS
					Executive function–Raven[36]	24	15.6 (15.5)	+1.0 (+1.0)	NS (NS)	0	NS
					Word fluency–animals, No. of nouns[37]	ND	17.6 (17.4)	0.0 (–0.9)	NS (NA)	+0.9	NS
					Word fluency–letter, No. of nouns[37]	ND	16.2 (15.2)	–0.7 (+2.3)	<.05 (<.05)	–3.0	NS

(continued)

of studies, number of participants, quality, applicability, and summarized results of the evidence for the effects of B vitamin intervention on neurocognitive conditions.

VITAMIN B_6

Three trials of either good, fair, or poor quality and of narrow to moderate applicability investigated the effect of B_6 intervention on cognitive function in people with either normal cognitive function or limited to those with ischemic vascular disease (**Table 2**).[8-10] Sample sizes ranged from about 19 to 88 participants taking vitamin B_6 supplements; doses ranged from 12 to 75 mg/d, considerably higher than the US Recommended Daily Allowance (RDA) dose of 1.3 to 1.7 mg/d. Vitamin B_6 supplementation was given for 5 or 12 weeks; however, notably, 1 study performed follow-up cognitive testing at 1 year, 9 months after the vitamin supplementation stopped.[8]

Across studies, among 9 different cognitive function subtests used in the 3 trials, no statistically significant difference in testing was found after vitamin B_6 supplementation in all but 1 test (Deijen et al[10]), where there was a significant improvement in long-term memory with vitamin B_6 compared with placebo. Among all the subtests, there was no consistent direction (net im-

Table 3. Effect of Cyanocobalamin or Hydroxycobalamin (Vitamin B_{12}) Intervention on Cognitive Function Tests in Randomized Controlled Trials (cont)

Source	Dose (Duration)	B Vitamin Participants (Controls), No.	Population Characteristic (Mean Age, y)	Quality/ Applicability	Test	Maximum Score*	Intervention (Control) Base Value	Intervention (Control) Change		Net Change	
								Value	*P* Value	Value	*P* Value
Bryan et al,[9] 2002	0.015 mg/d, oral (5 wk)	~19 (~19)‖	Normal (74)	Fair/narrow	Digit-symbol coding (WAIS)[22]	ND	62.5 (62.3)	+6.9 (+4.8)	NS (NS)	+2.1	NS
					Vocabulary (WAIS)[22]	ND	23.3 (21.9)	−0.3 (−0.5)	NS (NS)	+0.2	NS
					Digit span–backward (WAIS)[22]	ND	6.7 (7.1)	+0.2 (+0.4)	NS (NS)	−0.2	NS
					Stroop[23]	ND	2.50 (2.51)	−0.03 (−0.03)	NS (NS)	+0.09	NS
					Verbal fluency–initial letter[24]	ND	29.3 (23.7)	−0.1 (+3.3)	NS (NS)	−3.4	NS
Seal et al,[12] 2002	0.01 mg/d, oral (~4 wk)	10	Normal, with low serum vitamin B_{12} levels¶ (82)	Fair/narrow	MMSE[26]	30	15.4	0.0	ND	−1.6	NS
	0.05 mg/d, oral (~4 wk)	10 (11)	Normal, with low serum vitamin B_{12} levels¶ (82)	Fair/narrow	MMSE[26]	30	19.7 (19.6)	+1.0 (+1.6)	ND (ND)	−0.6	NS
Kwok et al,[13] 1998	1 mg/mo,# injection (3-6 mo)	27 (23)	Normal, with low serum vitamin B_{12} levels**(77)	Poor/ moderate	MMSE[26]	30	22.2 (23.8)	+0.1 (+0.2)	NS (NS)	−0.1	NS
					Digit span (WAIS-R)[22]	ND	10.4 (11.6)	+0.3 (−1.0)	NS (NS)	+1.3	NS
					Visual memory[22]	ND	12.7 (15.3)	−3.0 (−3.7)	NS (NS)	+0.7	NS
					Verbal memory[22]	ND	7.8 (11.4)	−1.1 (−2.1)	NS (NS)	+1.0	NS
					Verbal IQ[22]	ND	58.2 (60.1)	+1.1 (−1.2)	NS (NS)	+2.3	NS
					Performance IQ[22]	ND	74.9 (84.3)	+5.8 (−1.5)	.005 (NS)	+7.3	NS
Kral et al,[14] 1970	0.1 mg/d, 5 d/wk, injection (14 wk)	18 (22)	Normal (ND)	Poor/narrow	Memory quotient[38]	100	90 (88)	−3 (+4)	NS (ND)	−7	NS
					Lower limit of retention[39]	ND	38 (45)	−12 (−4)	NS (NS)	−8	NS
					Upper limit of retention[39]	ND	48 (45)	−6 (−5)	NS (NS)	−1	NS

Abbreviations: CAMCOG, the cognitive (COG) and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly Examination (CAMDEX) (assesses orientation, language, memory, praxis, attention, abstract thinking, perception, and calculation) (includes the Mini-Mental State Examination [MMSE]); IQ, intelligence quotient; MS, millisecond; ND, no data; NS, nonsignificant; Stroop, Stroop Color-Word Test; WAIS, Wechsler Adult Intelligence Scale; WAIS-R, WAIS–Revised.

*Unless otherwise indicated, higher score indicates better cognitive function.
†Intervention lasted 4 weeks; follow-up cognitive testing occurred at 3 months.
‡Placebo better than B vitamin.
§Lower score indicates better cognitive function.
‖Seventy-five participants were randomized among vitamins B_6, B_{12}, folic acid, and placebo.
¶Between 136 and 203 pg/mL (100-150 pmol/L).
#One milligram 3 times in week 1, then 1 mg/wk for 3 weeks, then 1 mg/mo.
**Less than 163 pg/mL (<120 pmol/L).

provement vs net worsening) of effect with supplementation.

There is inadequate evidence to support any dose effect of vitamin B_6 on the outcomes. There was insufficient evidence from the trials regarding differences in effect on tests of different cognitive domains. No other interactions were reported in the studies.

VITAMIN B_{12}

Six trials of variable quality assessed the effect of vitamin B_{12} intervention on cognitive function in humans (**Table 3**).[9,11-14,29] All studies had narrow to moderate applicability. Sample sizes ranged from 18 to 70 participants receiving vitamin B_{12}. Two trials each recruited cognitively intact participants with normal or low vitamin B_{12} levels; 1 trial included participants with cognitive impairment; and 1 included people with a range of cognitive function. The 6 trials used different doses and administration routes of vitamin B_{12} interventions ranging from 0.01 mg/d orally to 1 mg/wk intramuscularly. Three trials used oral vitamin B_{12}, and 3 used intramuscular vitamin B_{12}. Doses were higher than the US RDA of 2.4 µg/d. The duration of supplementation ranged from 4 weeks to 6 months. Notably, Hvas et al[11] retested cognitive function 2 months after stopping vitamin B_{12} supplementation. There was large heterogeneity among trials in the cognitive function assessment instruments used.

For most of the cognitive tests performed, no effect was found for vitamin B_{12}. Only 3 of the 35 cognitive function tests and subtests showed a statistically significant difference between participants receiving vitamin B_{12} compared with placebo. Notably, statistically significant net worsening on cognitive functioning tests was found in 2 studies (Hvas et al[11] and Eussen et al[29]). However, in 1 of these tests, the effect was driven primarily by a statistically significant improvement in the placebo arm that was not seen in the treatment arm.[11] Neither study considered the effects to be clinically significant. In contrast, a large nonsig-

Table 4. Effect of Folic Acid Intervention on Cognitive Function Tests

Source	Dose, mg/d (Duration)	B Vitamin Participants (Controls), No.	Population Characteristic (Mean Age, y)	Quality/ Applicability	Test	Maximum Score*	Intervention (Control) Base Value	Intervention (Control) Change		Net Change	
								Value	*P* Value	Value	*P* Value
Fioravanti et al,[15] 1997	15 (60 d)	16 (14)	Cognitive impairment, low folate levels† (80)	Fair/moderate	Acquisition and recall‡	ND	55.3 (62.1)	+4.2 (–1.2)	ND (ND)	+5.5	<.007
					Delayed recall‡	ND	56.1 (63.0)	+7.4 (0.0)	ND (ND)	+7.4	<.007
					Memory index‡	ND	49.3 (57.1)	+6.8 (+0.5)	ND (ND)	+6.3	<.002
					Encoding‡	ND	4.3 (5.3)	+0.5 (–0.2)	ND (ND)	+0.7	<.005
					Cognitive efficiency‡	ND	3.28 (4.25)	+0.63 (+0.06)	ND (ND)	+0.57	NS
					Attention efficiency‡	ND	6.40 (6.83)	+1.12 (+0.07)	<.05 (NS)	+0.97	NS
Bryan et al,[9] 2002	0.75 (5 wk)	~19 (~19)§	Normal (74)	Fair/narrow	Digit-symbol coding, 120 s (WAIS-R)[22]	ND	62.5 (62.3)	+6.9 (+4.8)	ND (ND)	+2.1	NS
					Digit span–backward (WAIS-R)[22]	ND	6.7 (7.1)	+1.7 (+0.4)	ND (ND)	+1.3	NS
					Executive function (Stroop)[23]	ND	2.50 (2.51)	–0.03 (–0.12)	ND (ND)	+0.09	NS
					Verbal fluency–initial letter[24]	ND	29.3 (23.7)	–0.1 (+3.3)	ND (ND)	–3.4	NS
					Verbal ability–vocabulary[24]	ND	23.3 (21.9)	–0.3 (–0.1)	ND (ND)	–0.1	NS
Sommer et al,[16] 2003	20 (10 wk)	4 (3)	Dementia, with normal folate levels (77)	Poor/narrow	Memory scale–logical memory subtest (WAIS-R)[30]	ND	4.9 (4.6)	0.0 (+1.7)	ND (ND)	–1.7	NS
					Memory scale–associate learning subtest (WAIS-R)[30]	ND	16.6 (11.0)	–7.8 (+0.3)	ND (ND)	–7.5	.08‖
					WAIS-R prorated verbal IQ (WAIS-R)[30]	ND	107.8 (110.0)	–2.5 (+12.5)	ND (ND)	+10.0	NS
					Boston naming test[40]	ND	40.8 (42.3)	+1.2 (+1.4)	ND (ND)	–0.2	NS
					Controlled oral word association test[41]	ND	29.5 (36.0)	+3.3 (–5.0)	ND (ND)	+8.3	NS
					Speed/concentration–Trails A[32]	ND	233 (278)	+15 (–17)	ND (ND)	+32	NS
					Speed/concentration–Trails B[32]	ND	373 (412)	+20 (–55)	ND (ND)	+75	.08
					Speed/concentration–finger-tapping test[42]	ND	38.4 (32.7)	–1.5 (–8.4)	ND (ND)	+6.9	NS

Abbreviations: ND, no data; NS, nonsignificant; Stroop, Stroop Color-Word Test; WAIS-R, Wechsler Adult Intelligence Scale–Revised.
*Higher score indicates better cognitive function.
†Lower than 3 ng/mL (<6.8 nmol/L).
‡Part of the Randt memory test.[43]
§Seventy-five participants were randomized among vitamins B_6, B_{12}, folic acid, and placebo.
‖Placebo better than B vitamin.

nificant improvement was reported in 1 test,[13] in which a statistically significant change compared with baseline was found with treatment, but the net change failed to reach statistical significance.

Seal et al[12] directly evaluated the effect of vitamin B_{12} oral supplementation in 2 intervention arms, one receiving double the dose of the other, and compared these groups with placebo. No significant change was found in Mini-Mental State Examination[26] scores when the 3 groups were compared.

There is large heterogeneity among trials in terms of dose, administration route, and duration of treatment, and it would be difficult to support any conclusion about a potential dose effect. Overall, half of the tests found a net improvement in cognitive function and half a net worsening of cognitive function with vitamin B_{12} supplementation. There was no evidence across trials of differences in effect in tests of different cognitive domains.

FOLIC ACID

Three trials of moderate to poor quality reported data on folic acid supplementation and the effect on cognitive function or therapeutic benefit in a total of 39 people who received folic acid (**Table 4**).[9,15,16] Two trials were conducted among participants with dementia or cognitive impairment, and 1 among normal participants. The trials tested various doses of folic acid ranging from 0.75 to 20 mg/d. In comparison, the US RDA for folate is 0.4 to 1 mg/d. Trial durations ranged from 5 to 10 weeks.

The 3 trials had discordant results in 3 different populations. In a trial of relatively low-dose folic acid supplementation (0.75 mg/d) in women with normal cognitive function,[9] no significant effects were found across 5 measured tests, with 3 showing a net improvement and 2 a net worsening. In a very small trial of folic acid, 20 mg/d, in 7 people with dementia and normal baseline folate levels,[16] no statistically significant difference was found in the results of 8 cognitive function tests, although there was a trend toward a net worsening of associate learning and a trend toward a net improvement in 1 concentration test (Trails B[32]). Overall, 5 tests found a net improvement and 3 a net worsening of cognitive function. In the third trial of cognitively impaired individuals with low baseline folate

Table 5. Effect of Combination Interventions on Cognitive Function

Source, y	Dose, mg/d FA	B_6	B_{12}	Duration	B Vitamin Participants (Controls), No.	Population Characteristic (Mean Age, y)	Quality/ Applicability	Test	Maximum Score*	Base Value	Intervention (Control) Change Value	*P* Value	Net Change Value	*P* Value
McMahon et al,[44] 2006	1.0	10.0	0.5 (Oral)	2 y	125 (124)	Normal (73)	Good/wide	MMSE[26]	30	29.2 (29.2)	+0.1 (+0.2)	ND (ND)	−0.09	NS
								Wechsler paragraph recall test[22]	50	22.5 (23.4)	−3.8 (−2.7)	ND (ND)	−0.88	NS
								Category word fluency test, total words in 3 minutes[45]	ND	54.2 (55.8)	+11.6 (+13.0)	ND (ND)	−0.86	NS
								Rey auditory verbal learning test trials I-V[45]	75	42.1 (42.6)	+1.8 (+1.6)	ND (ND)	−0.98	NS
								Rey auditory verbal learning test trials VI[45]	15	7.8 (7.7)	−0.5 (−0.2)	ND (ND)	−0.35	NS
								Raven progressive matrices[36]	20	14.2 (14.2)	−2.6 (−2.3)	ND (ND)	−0.31	NS
								Controlled oral word association test[41]	ND	37.6 (39.3)	+2.5 (+1.7)	ND (ND)	+0.31	NS
								Reitan trail-making test, part B[32]	ND†	104.8 (100.7)	+9.6 (−1.7)	ND (ND)	+1.08	.007
Stott et al,[8] 2005	2.5	NG	0.5 (Oral)	3/12 mo‡	85/73 (82/73)§	Ischemic vascular disease (74)	Good/ narrow	Telephone interview for cognitive status[20]	39	25.5 (I&C)	−0.5 (+0.3)	NS (NS)	−0.8	NS
								Letter-digit coding test[21]	ND	19.7 (I&C)	−0.85 (+0.1)	NS (NS)	−0.9	NS
Lewerin et al,[17] 2005	0.8	3.0	0.5 (Oral)	4 mo	115 (64)	Normal (76)	Fair/wide	Digit span–forward (WAIS)[46]	9	5.8 (5.9)	+0.2 (+0.3)	.09 (NS)	−0.1	NS
								Digit span–backward (WAIS)[46]	8	4.4 (4.6)	+0.25 (+0.22)	.09 (NS)	+0.03	NS
								Block design (WAIS)[46]	42	18.5 (20.0)	+1.0 (+0.8)	NS (NS)	+0.2	NS
								Digit symbol (WAIS)[46]	90	35.1 (38.0)	+0.9 (+2.3)	NS (NS)	−1.4	.09‖
								Identical forms[47]	60	23.3 (24.8)	+0.1 (+1.5)	NS (NS)	−1.4	.04‖
								Visual reproduction[38]	14	6.9 (7.0)	+0.6 (+0.6)	NS (NS)	0	NS
								Synonyms[47]	30	22.5 (22.4)	+0.31 (+1.3)	NS (NS)	−1.0	.02‖
								Thurstone picture memory test[48]	28	20.3 (21.1)	+1.7 (+2.4)	NS (NS)	−0.7	NS
								Figure classification[48]	30	15.8 (16.8)	+1.5 (+0.6)	NS (NS)	+0.9	NS
Eussen et al,[29] 2006	0.4	NG	1 (Oral)	24 wk	66 (65)	Normal to cognitive impairment (73)	Fair/ moderate	Digit span–forward (WAIS)[22]	16	7.5 (7.6)	−0.1 (+0.2)	NS (NS)	−0.3	NS
								Digit span–backward (WAIS)[22]	14	5.1 (4.7)	−0.2 (+0.6)	<.05 (<.05)	−0.8	.001‖
								Executive function similarities (WAIS)[30]	12	4.7 (4.8)	+1.1 (+0.6)	NS (NS)	+0.5	NS
								Speed–finger tapping, ms[31]	ND†	442 (409)	−17 (−20)	NS (NS)	+3	NS
								Speed–trail-making test, part A, s[32]	ND†	76.9 (72.0)	−7.1 (+1.9)	NS (NS)	−9.0	NS
								15-Word learning–immediate recall[33]	75	30.1 (30.0)	+6.2 (+5.7)	NS (NS)	+0.5	NS
								15-Word learning–delayed recall[33]	15	4.6 (5.1)	+1.5 (+1.0)	NS (NS)	+0.5	NS
								15-Word learning–recognition[33]	30	26.6 (25.3)	+0.8 (+1.7)	<.05 (<.05)	−0.9	.03‖
								Executive function–trail-making test, part C/part A[32]	ND†	2.7 (2.9)	+0.4 (−0.1)	NS (NS)	+0.5	NS
								Executive function–Stroop test, part 3/part 2[34]	ND†	2.2 (2.1)	0.0 (+0.7)	NS (NS)	−0.7	NS

(continued)

Table 5. Effect of Combination Interventions on Cognitive Function (cont)

Source, y	Dose, mg/d FA	B_6	B_{12}	Duration	B Vitamin Participants (Controls), No.	Population Characteristic (Mean Age, y)	Quality/ Applicability	Test	Maximum Score*	Base Value	Intervention (Control) Change Value	*P* Value	Net Change Value	*P* Value
Eussen et al,[29] 2006	0.4	NG	1 (Oral)	24 wk	66 (65)	Normal to cognitive impairment (73)	Fair/ moderate	Executive function–Raven[36]	24	15.2 (15.5)	+1.5 (+1.0)	NS (NS)	+0.5	NS
								Word fluency, animals, No. of nouns[37]	ND	17.6 (17.4)	–0.3 (–0.9)	NS (NS)	+0.6	NS
								Word fluency, letters, No. of nouns[37]	ND	15.5 (15.2)	+0.5 (+2.3)	<.05 (<.05)	–1.8	NS
Clarke et al,[18] 2003	2	NG	1 (Oral)	12 wk	128¶	Dementia (75)	Poor/ moderate	MMSE[26]	30	21 (I&C)	Not significantly altered by treatment			
								ADAS[49]	70†	27 (I&C)	Not significantly altered by treatment			
Shaw et al,[19] 1971	15	NG	1# (Injection)	12 wk	17¶	Severe dementia (81)	Poor/narrow	Dementia scale[50]	ND	ND	The means were unchanged in both groups			
								Blessed Information–Memory Concentration Test[51]	ND	ND	Increment not statistically significant			

Abbreviations: ADAS, Alzheimer Disease Assessment Scale; B_6, pyridoxine hydrochloride (vitamin B_6,); B_{12}, cyanocobalamin or hydroxycobalamin (vitamin B_{12}); FA, folic acid; I&C, intervention and control groups not reported separately; MMSE, mini-mental state examination; ND, no data; NG, not given; NS, nonsignificant; WAIS, Wechsler Adult Intelligence Scale.

*Higher score indicates better cognitive function unless otherwise noted.

†Lower score indicates better cognitive function.

‡Intervention lasted 12 weeks; follow-up cognitive testing occurred at 1 year.

§Number tested with telephone interview for cognitive status[20]/number tested with letter-digit coding test.[21]

||Placebo better than B vitamin.

¶No data on how many participants in each arm.

#Hydroxycobalamin, 1000 mg/d for the first week and then 100 mg/wk for 11 weeks thereafter.

levels,[15] supplementation with folic acid, 15 mg/d, resulted in a net benefit in all 6 cognitive tests used, 4 of which were statistically significant. The study found that the cognitive improvement after folic acid intervention was correlated in a linear fashion with the low levels of folate at baseline.

Owing to the paucity of evidence evaluating the effect of folic acid on the outcomes, any conclusions remain tentative. Nevertheless, the limited evidence may suggest a benefit from folic acid supplementation for people with both cognitive impairment and serum folate levels lower than 3 ng/mL (<6.8 nmol/L).

COMBINED B VITAMINS

Six trials of varying quality reported data on the effect of combined B vitamin intervention in participants with dementia, normal cognitive function, or ischemic vascular disease (**Table 5**).[8,17-19,29,44] All trials used different daily doses of various B vitamins; all substantially higher than the US RDA for each vitamin. Studies tested combination B vitamins in from 17 to 128 participants. Two studies used a combination of folic acid, vitamin B_6, and vitamin B_{12}[17,44]; the other 4 trials combined folic acid and vitamin B_{12}.[8,18,19,29] One study used vitamin B_{12} injections and oral folic acid,[19] while the other trials used oral vitamin B_{12}. One study lasted 2 years[44]; in the others, the B vitamin supplements were given for either 3 or 4 months; though 1 trial tested cognitive function 9 months after ending treatment.[8]

For most of the cognitive tests, no effect was found with B vitamin treatment. In 2 studies,[17,29] participants in the placebo arm performed better than those receiving B vitamins in 5 of the 25 tests. In contrast, McMahon et al[44] found a significant improvement in 1 of 8 cognitive tests with a combination of all 3 B vitamins. The remaining 3 trials of combination folic acid and vitamin B_{12} found no significant effects on cognitive testing, although 2 did not report quantitative data.[8,18,19]

There were no dose-related responses discussed in the trials. There was no evidence across trials of differences in effect on tests of different cognitive domains.

COMMENT

The limited evidence from the short-duration randomized controlled trials suggests that supplementation with vitamins B_6 or B_{12} or folic acid among either elderly cognitively intact individuals or those with dementia or cognitive impairment does not improve cognitive function as measured by a wide battery of tests. The 1 exception to this may be folic acid supplementation in people with both cognitive impairment and serum folate levels lower than 3 ng/mL (<6.8 nmol/L). However, any conclusions about the effect of folic acid treatment are greatly limited because there are only 3 trials with 39 people who received folic acid. Further clarification may be available soon because a large, 3-year trial of folic acid in elderly people with hy-

perhomocysteinemia has been presented at an international conference.[52] The abstract, which has not yet been peer reviewed, preliminarily reported a net improvement in global cognitive function including memory, sernsorimotor speed, and informational processing speed.

Notably, in a minority of studies of both vitamin B_{12} and combinations of B vitamins that include vitamin B_{12} compared with placebo, the B vitamin treatment resulted in worse performance on a small number of cognitive tests. The clinical significance of this effect, though, is questionable, in that those receiving placebo had statistically significant improvements from baseline among these tests.

Overall, the data are sparse, and firm conclusions are not possible. Importantly, no trial evaluated the risk of developing dementia, clinical symptoms, neurological imaging tests, or clinical outcomes beyond ability to perform cognitive function tests. About 50 different tests or subtests were used across the trials, measuring different or overlapping domains of cognitive function; thus, comparisons across studies were difficult. In addition, studies did not explicitly report the clinical importance of the changes in cognitive function test results. Consequently, clinical inferences based on the reported scores alone would be problematic.

Only 1 trial compared different doses of vitamin B_{12}, and only 2 directly compared the different B vitamins.[8,9] No trial directly compared populations, routes of administration of vitamin B_{12}, or different durations. In addition, the small number of available trials limited our ability to assess the impact of these factors. The quality of the trials was often compromised by incomplete reporting of methodology and results, lack of blinding, small sample size, short duration, and other factors. Two of the trials also implicitly tested the effect of short-term intervention (1 or 3 months) on longer-term cognitive function (3 or 12 months).[8,11] Interpretation of the clinical value of this type of trial is unclear.

Future well-performed, well-analyzed, sufficiently powered, long-term, randomized controlled trials are necessary to address whether B vitamin supplementation is effective to slow cognitive decline or improve cognitive function. No peer-reviewed trial has addressed the question of whether these B vitamins can prevent or delay clinical dementia or can affect clinical symptoms of dementia. However, further standardization is clearly needed both in the field of vitamin research and for the assessment of cognitive function. Future studies should use only well-established diagnostic criteria for neurocognitive disorders and only measures of cognitive function that have been verified and accepted by the neurocognitive research community. Studies that use nonstandard diagnostic definitions or neurocognitive tests are of lesser value to clinicians, policy makers, and other researchers. Researchers should also preferentially use cognitive function tests that adequately differentiate between different cognitive domains and should evaluate how B vitamin supplementation differentially affects different cognitive domains. In addition, imaging studies such as magnetic resonance imaging and positron-emission tomography may prove to be of value to assess how B vitamin supplementation affects cognitive function.

In conclusion, the few available randomized controlled trials of vitamins B_6, and B_{12} and folic acid supplementation, alone or in combination, do not provide adequate evidence for a beneficial effect of supplementation on cognitive function testing in people with either normal or impaired cognitive function, although 1 very small trial found an improvement with folic acid supplementation in patients with low baseline folate levels. However, the poor quality and the small number of trials and participants preclude a firm conclusion. Additional trials are needed to determine which populations, if any, would benefit from B vitamin supplementation and to determine whether B vitamin supplementation would affect clinical signs and symptoms of dementia.

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REFERENCES

1. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet.* 2005;366:2112-2117.
2. Herrmann N. Cognitive pharmacotherapy of Alzheimer's disease and other dementias. *Can J Psychiatry.* 2002;47:715-722.
3. Wardlaw GM, Kessel M. *The Water-Soluble Vitamins: Perspectives in Nutrition.* 5th ed. New York, NY: McGraw-Hill; 2002:364-417.
4. Riggs KM, Spiro A III, Tucker K, Rush D. Relations of vitamin B-12, vitamin B-6, folate, and homocysteine to cognitive performance in the Normative Aging Study. *Am J Clin Nutr.* 1996;63:306-314.
5. Wang HX, Wahlin A, Basun H, Fastbom J, Winblad B, Fratiglioni L. Vitamin B(12) and folate in relation to the development of Alzheimer's disease. *Neurology.* 2001;56:1188-1194.
6. Balk E, Chung M, Raman G, et al. *B Vitamins and Berries and Age-Related Neurodegenerative Disorders: Evidence Report/Technology Assess-*

ment No. 134. Rockville, Md: Agency for Healthcare Research and Quality; April 2006.
7. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(suppl 1):S1-S266.
8. Stott DJ, MacIntosh G, Lowe GD, et al. Randomized controlled trial of homocysteine-lowering vitamin treatment in elderly patients with vascular disease. *Am J Clin Nutr*. 2005;82:1320-1326.
9. Bryan J, Calvaresi E, Hughes D. Short-term folate, vitamin B-12 or vitamin B-6 supplementation slightly affects memory performance but not mood in women of various ages. *J Nutr*. 2002;132: 1345-1356.
10. Deijen JB, van der Beek EJ, Orlebeke JF, van den Berg H. Vitamin B-6 supplementation in elderly men: effects on mood, memory, performance and mental effort. *Psychopharmacology (Berl)*. 1992; 109:489-496.
11. Hvas AM, Juul S, Lauritzen L, Nexo E, Ellegaard J. No effect of vitamin B-12 treatment on cognitive function and depression: a randomized placebo controlled study. *J Affect Disord*. 2004; 81:269-273.
12. Seal EC, Metz J, Flicker L, Melny J. A randomized, double-blind, placebo-controlled study of oral vitamin B12 supplementation in older patients with subnormal or borderline serum vitamin B12 concentrations. *J Am Geriatr Soc*. 2002;50:146-151.
13. Kwok T, Tang C, Woo J, Lai WK, Law LK, Pang CP. Randomized trial of the effect of supplementation on the cognitive function of older people with subnormal cobalamin levels. *Int J Geriatr Psychiatry*. 1998;13:611-616.
14. Kral VA, Solyom L, Enesco H, Ledwidge B. Relationship of vitamin B12 and folic acid to memory function. *Biol Psychiatry*. 1970;2:19-26.
15. Fioravanti M, Ferrario E, Massaia M, et al. Low folate levels in the cognitive decline of elderly patients and the efficacy of folate as a treatment for improving memory deficits. *Arch Gerontol Geriatr*. 1997;26:1-13.
16. Sommer BR, Hoff AL, Costa M. Folic acid supplementation in dementia: a preliminary report. *J Geriatr Psychiatry Neurol*. 2003;16:156-159.
17. Lewerin C, Matousek M, Steen G, Johansson B, Steen B, Nilsson-Ehle H. Significant correlations of plasma homocysteine and serum methylmalonic acid with movement and cognitive performance in elderly subjects but no improvement from short-term vitamin therapy: a placebo-controlled randomized study. *Am J Clin Nutr*. 2005; 81:1155-1162.
18. Clarke R, Harrison G, Richards S; Vital Trial Collaborative Group. Effect of vitamins and aspirin on markers of platelet activation, oxidative stress and homocysteine in people at high risk of dementia. *J Intern Med*. 2003;254:67-75.
19. Shaw DM, Macsweeney DA, Johnson AL, et al. Folate and amine metabolites in senile dementia: a combined trial and biochemical study. *Psychol Med*. 1971;1:166-171.
20. Gallo JJ, Breitner JC. Alzheimer's disease in the NAS-NRC Registry of aging twin veterans, IV: performance characteristics of a two-stage telephone screening procedure for Alzheimer's dementia. *Psychol Med*. 1995;25:1211-1219.
21. Houx PJ, Shepherd J, Blauw GJ, et al. Testing cognitive function in elderly populations: the PROSPER study: PROspective Study of Pravastatin in the Elderly at Risk. *J Neurol Neurosurg Psychiatry*. 2002; 73:385-389.
22. Wechsler D. *Wechsler Adult Intelligence Scale*. 3rd ed. San Antonio, Tex: Psychological Corp; 1997.
23. Dodrill CB. A neuropsychological battery for epilepsy. *Epilepsia*. 1978;19:611-623.
24. Benton AL, Hamsher D. *Multilingual Aphasia Examination*. Iowa City: University of Iowa; 1989.
25. Emmen HH, Hogendijk EMG, Hooisma J, Orlebeke JF, Uijtdehaage SHJ. *Adaption of Two Standardized International Test Batteries for Use in the Netherlands for Detection of Exposure to Neurotoxic Compounds: Internal Report*. Rijswijk, the Netherlands: Medisch Biologisch Laboratorium TNO; 1988.
26. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
27. Roth M, Tym E, Mountjoy CQ, et al. CAMDEX: a standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *Br J Psychiatry*. 1986;149:698-709.
28. Nielsen H, Lolk A, Krag-Sorensen P. Normative data for eight neuropsychological tests, gathered from a random sample of Danes aged 64-83 years. *Nord Psykol*. 1995;47:241-255.
29. Eussen SJ, de Groot LC, Joosten LW, et al. Effect of oral vitamin B-12 with or without folic acid on cognitive function in older people with mild vitamin B-12 deficiency: a randomized, placebo-controlled trial. *Am J Clin Nutr*. 2006;84:361-370.
30. Wechsler D. *Wechsler Adult Intelligence Scale–Revised Manual*. New York, NY: Psychological Corp, Harcourt Brace & Jovanovich; 1982.
31. Houx P. *Cognitive Aging and Health-Related Factors*. Maastricht, the Netherlands: Maastricht University; 1991.
32. Reitan RM. *Trail Making Test: Manual for Administration and Scoring*. Tucson, Ariz: Reitan Neuropsychological Laboratory; 1992.
33. Saan RJ, Deelman BJ. *New 15-Words Test (A and B): A Manual*. Lisse, the Netherlands: Swets & Zeitlinger; 1986.
34. Houx PJ, Jolles J, Vreeling FW. Stroop interference: aging effects assessed with the Stroop Color-Word Test. *Exp Aging Res*. 1993;19:209-224.
35. Visser RH. *Manual of the Complex Figure Test*. Lisse, the Netherlands: Swets & Zeitlinger; 1985.
36. Raven J. *Guide to Using the Colored Progressive Matrices*. London, England: HK Lewis; 1965.
37. Luteijn FvdPF. *Manual Groningen Intelligence Test*. Lisse, the Netherlands: Swets & Zeitlinger; 1983.
38. Wechsler D. Standardized memory scale for clinical use. *J Psychol*. 1945;19:87.
39. Cameron DE. Impairment in the retention phase of remembering. *Psychiatr Q*. 1943;17:395.
40. Kaplan E, Goodglass H, Weintraub S. *The Boston Naming Test*. Philadelphia, Pa: Lea & Febiger; 1983.
41. Benton AL, Hamsher K, Sivan AB. *Multilingual Aphasia Examination*. Iowa City, Iowa: AJA Associates; 1994.
42. Reitan RM. *Clinical Neuropsychology: Current Status and Applications*. New York, NY: Hemisphere; 1974.
43. Randt CT, Brown ER. *Randt Memory Test*. Bayport, NY: Life Science Associates; 1983.
44. McMahon JA, Green TJ, Skeaff CM, Knight RG, Mann JI, Williams SM. A controlled trial of homocysteine lowering and cognitive performance. *N Engl J Med*. 2006;354:2764-2772.
45. Lezak MD. *Neuropsychological Assessment*. 3rd ed. New York, NY: Oxford University Press; 1995.
46. Wechsler D. *The Measurement and Appraisal of Adult Intelligence*. Baltimore, Md: Williams & Wilkins; 1958.
47. Dureman I, Salde H. *Psychometric and Experimental Psychological Methods for Clinical Application* [in Swedish]. Stockholm, Sweden: Almquist & Wiksell; 1959.
48. Thurstone L. *Primary Mental Abilities: Psychometric Monographs*. Chicago, Ill: University of Chicago Press; 1938.
49. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984; 141:1356-1364.
50. Kendrick DC. A cross-validation study of the use of the SLT and DCT in screening for diffuse brain pathology in elderly subjects. *Br J Med Psychol*. 1967;40:173-178.
51. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry*. 1968;114: 797-811.
52. Durga J. Effect of 3-year folic acid supplementation on cognitive function in older adults: a randomized double blind controlled trial [abstract]. *J Nutr Health Aging*. 2006;10:204-214.