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B Vitamins and Berries and Age-Related Neurodegenerative Disorders

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public-and private-sector organizations in their efforts to improve the quality of health care in the United States. This report on B Vitamins and Berries and Age-Related Neurodegenerative Disorders was requested and funded by the National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Dietary Supplements (ODS), National Institutes of Health. The reports and assessments provide organizations with comprehensive, science-based information on common, relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of the evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality and improvement projects throughout the nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent to the Task Order Officer below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov.**

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Structured Abstract

Objectives. To assess the effects, associations, mechanisms of action, and safety of B vitamins and, separately, berries and their constituents on age-related neurocognitive disorders – primarily Alzheimer's (AD) and Parkinson's disease (PD).

Data Sources. MEDLINE® and CAB Abstracts™. Additional studies were identified from reference lists and technical experts.

Review Methods. Vitamins B1, B2, B6, B12, and folate, and a dozen types of berries and their constituents were evaluated. Human, animal, and in vitro studies were evaluated. Outcomes of interest from human studies were neurocognitive function or diagnosis with AD, cognitive decline, PD, or related conditions. Intervention studies, associations between dietary intake and outcomes, and associations between B vitamin levels and outcomes were evaluated. Specific mechanisms of action were evaluated in animal and in vitro studies. Studies were extracted for study design, demographics, intervention or predictor, and neurocognitive outcomes. Studies were graded for quality and applicability.

Results. In animal studies, deficiencies in vitamins B1 or folate generally cause neurological dysfunction; supplementation with B6, B12, or folate may improve neurocognitive function. In animal experiments folate and B12 protect against genetic deficiencies used to model AD; thiamine and folate also affect neurovascular function and health.

Human studies were generally of poor quality. Weak evidence suggests possible benefits of B1 supplementation and injected B12 in AD. The effects of B6 and folate are unclear. Overall, dietary intake studies do not support an association between B vitamin intake and AD. Studies evaluating B vitamin status were mostly inadequate due to poor study design. Overall, studies do not support an association between B vitamin status and age-related neurocognitive disorders.

Only one study evaluated human berry consumption, finding no association with PD. Animal studies of berries have almost all been conducted by the same research group. Several berry constituents have been shown to affect brain and nerve tissue function. Blueberry and strawberry extract were protective of markers of disease, although effects on neurocognitive tests were less consistent. Berry extracts may protect against the deleterious effects of compounds associated with AD.

Reporting of adverse events was uncommon. When reported, actual adverse events from B vitamins were rare and minor.

Conclusions. The current research on B vitamins is largely inadequate to confidently assess their mechanisms of action on age-related neurocognitive disorders, their associations with disease, or their effectiveness as supplements. B vitamin supplementation may be of value for neurocognitive function, but the evidence is inconclusive.

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The Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/berry/berry.pdf

Executive Summary

Introduction

Disorders of the nervous system account for more long-term care, chronic suffering, and diminished quality of life than all other disorders combined. Age-related neurodegenerative disorders are chronic and progressive conditions that result from loss of the maintenance of neurons involved in cognitive, emotional, motor and sensory functions. The two most common age-related neurodegenerative disorders are Alzheimer's (AD) and Parkinson's diseases (PD). This report investigates the possible relationships both of B vitamin status and supplementation and of berry consumption with age-related neurodegenerative disorders.

This report was sponsored by the National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Dietary Supplements (ODS), National Institutes of Health.

Methods

Key Questions

B Vitamins

1. What is the evidence regarding mechanisms of action of the B vitamins B1, B2, B6, B12, and folate (singly and in combination) for preventing, decreasing the rate of progression of, or reversing the neurological changes associated with age-related neurodegenerative conditions such as Parkinson's or Alzheimer's disease?

2. What is the evidence that the B vitamins B1, B2, B6, B12, and folate can prevent, decrease the rate of progression of, or reverse the neurological changes associated with age-related neurodegenerative conditions such as Parkinson's or Alzheimer's disease in humans

3. What adverse events in humans have been reported in the literature for supplementation with the B vitamins B1, B2, B6, B12, and folate?
    a. Do the frequency of adverse events vary with source, dose, or other evaluated factors?

Berries

1. What are the constituents in berries with beneficial nerve- and brain-related health effects (from in vitro, animal, and human studies)?
    a. In what other food sources are these constituents found?

2. What is the evidence regarding mechanisms of action of berry constituents for preventing, decreasing the rate of progression of, or reversing the neurological changes associated with age-related neurodegenerative conditions, including Parkinson's or Alzheimer's disease?

3. What is the evidence that the constituents of berries can prevent, decrease the rate of progression of, or reverse the neurological changes associated with age-related neurodegenerative conditions, including Parkinson's or Alzheimer's disease in humans
    a. Is the source, species, dose, composition, characteristics, or processing of berries and berry constituents related to the effect of the intervention?

4. What adverse events in humans have been reported in the literature for the constituents in berries?
    a. Do the frequency of adverse events vary with source, dose, or other evaluated factors?

We reviewed all studies of berries and their constituents that addressed these questions, regardless of specific topic. However, for B vitamins we restricted the specific topics to the following:

B Vitamins: Human Studies

- Association between B vitamin treatment/intake with diagnosis or severity of AD or PD, cognitive function, or histopathology
- Association of B vitamin status and AD or PD diagnosis, histopathology, severity of disease, or cognitive function

B Vitamins: Animal / In Vitro Studies

- Effect of B vitamin supplementation or deficiency on cognitive function, movement disorders, histopathology, etc., in appropriate models
- Effect of B vitamins on the expression or function of AD-related genes
- Blood brain barrier and cerebrovascular endothelial function in relation to B vitamins

Approach To Analyzing the Literature

General Inclusion Criteria

Human studies. The common inclusion criteria for human studies consist of primary studies; English language publication, human adult subjects; analysis of the predictor or description, including quantification, of the intervention, and analysis of the following categories of outcomes: diagnosis or severity of AD, PD, other age-related neurocognitive disorders, or cognitive impairment; tests of cognitive function. We excluded other neuropsychiatric conditions and neuromotor diseases. For B vitamin interventions, we included only prospective trials.

Animal / in vitro studies. Animal and in vitro studies had to be published in full form in English language journals. We included all animal and in vitro models of diseases of interest and all outcome measurements related to the outcomes and/or associations of interest. We excluded studies that used inappropriate animal or in vitro models.

Literature Search Strategy. We conducted a comprehensive literature search to address the key questions. Final literature searches for English language publications on B vitamins and berries were conducted in MEDLINE® and the Commonwealth Agricultural Bureau (CAB)

Abstracts™ between February and March 2005. The searches included both human, animal, and in vitro studies.

Both the B vitamin and berry searches used a common neurocognitive model that included the following terms: nervous system diseases, cognitive disorders, neurodegeneration, dementia, Alzheimer, Parkinson, Lewy body, neuron/nerve cells, brain, and related terms.

Additional studies were sought by contacting members of the TEP, and from reference lists of selected included articles, review articles and meta-analyses.

Data Extraction. The same data extraction forms were used for both the B vitamin and berry articles. Standard data extraction forms were used for human studies. For animal and in vitro studies, data extraction focused more on study hypotheses and conclusions than on design and quantitative results.

Grading of the Evidence

We used a 3-category grading system (A, B, C) to denote the methodological quality of each study. This system, with variations in criteria, was used for both human and animal studies. Separate criteria were used for human intervention studies, human association studies, and animal studies to account for different issues related to these types of studies.

- **A** Category A studies have the least bias and results are considered valid.
- **B** Category B studies are susceptible to some bias, but not sufficient to invalidate the results.
- **C** Category C studies have significant bias that may invalidate the results.

Human studies were also assessed for applicability:

- 🚹🚹🚹 Sample is representative of the target population.
- 🚹🚹 Sample is representative of a relevant sub-group of the target population.
- 🚹 Sample is representative of a narrow subgroup of subjects only.

Results

B Vitamins

For B vitamins, 85 human studies and 17 animal or in vitro studies were evaluated. Although the review covers both neurocognitive function related to AD and related diseases and the movement disorders and motor systems degeneration related to PD and related diseases, only scant evidence was found regarding PD-related conditions.

Mechanisms of Action. Overall, research has shown that there were negative effects of thiamine, vitamin B6 and folate deficiency on animal's clinical status and/or histopathology, although not all deficient animals had worse performance in neurocognitive tests. Studies have found some positive effects of the supplementations of vitamin B6, vitamin B12, and folate on animal's performance in neurocognitive tests. Folate deficiency also showed a synergistic effect with both PD and AD pathology. Folate appears to protect against oxidative damage associated with ApoE gene knockout mouse models. Folate and B12 deficiency also induce presenilin-1, but do not appear to affect amyloid precursor protein. Thiamine (vitamin B1) is required for

active transport of pyruvate across the blood brain barrier and maintaining integrity and normal permeability of the blood brain barrier. Folate is protective against homocysteine-induced cerebrovascular damage.

B Vitamin Intervention Trials

Vitamin B1. Three randomized controlled trials (RCTs), one non-randomized comparative trial and one uncontrolled cohort study that assessed the effect of thiamine intervention among people with either probable or possible AD were heterogeneous in their outcomes. Most found improvements in cognitive function or a slowed rate of deterioration using some measures of cognitive testing, either compared to control or in uncontrolled studies. However, either no difference between treatment and control or no improvement with thiamine supplementation was found in all studies with other measures of cognitive function. Only the uncontrolled cohort study reported blood levels of thiamine before intervention and included AD subjects with normal levels.

Vitamin B2. No prospective trial has evaluated the effect of B2 treatment on neurocognitive function.

Vitamin B6. Only two RCTs of cognitively intact population investigated the effect of B6 intervention on cognitive function. Participants had B6 levels within normal range in both trials. With treatment, a significant improvement was found in one of the RCTs with one cognitive function test. No other significant change was reported in the studies.

Vitamin B12. Five RCTs, one non-randomized comparative trial, and seven cohort studies assessed the effect of B12 intervention on cognitive function. Seven of these studies recruited participants with low B12 levels, while the remaining five studies assessed individuals with normal B12 levels. There was a large degree of heterogeneity across the studies. Although several studies suggested some improvement in cognitive function, few reached statistical significance. Results were frequently conflicting. Vitamin B12 was given intramuscularly in the only RCT that found a significant effect in the treatment group compared with the controls. Similarly, only cohort studies that used intravenous or intramuscular vitamin B12 reported a significant effect on cognitive function scores. However, the lack of data directly comparing oral and injected routes of vitamin B12 and the paucity of controlled trials limits any conclusions regarding the utility of different routes of administration.

Folate. Three RCTs and two uncontrolled cohort studies reported data on the effect of folate intervention. One RCT of subjects with dementia and normal folate levels found worse neuropsychological scores in the folate treatment group among subjects with dementia. Two other studies, one RCT and one cohort study, found significant improvement with folate supplementation compared to placebo in different populations. The study of patients with PD found no therapeutic benefit. Three studies reported blood folate levels before intervention, of which only two studies (one RCT and one cohort study) included patients with low folate levels.

Combination of B vitamins. Three RCTs and three uncontrolled cohort studies assessed the effects of a combination of B vitamins as interventions on cognitive function. Each used different daily doses of various B vitamins including folate, B6, and B12. All but one found no significant change in cognitive function after combination B vitamin supplementation. Only one

RCT assessed the effects of combined vitamin intervention on patients with low blood folate levels; the remainder of the studies included patients with normal mean blood vitamin levels.

B Vitamin Dietary Intake Studies. Five longitudinal studies and five cross-sectional studies examined the association between the dietary intake levels of B vitamins and cognitive function or the risk of age-related neurodegenerative diseases. No significant associations were found between dietary intakes of B6 or B12 and PD, AD, cognitive function, or cognitive decline across three studies. One additional study found dietary intakes of B6 and B12 were positively associated with improvements in some, but not all, cognitive function measures. Two studies found opposite relationships between dietary intakes of folate and cognitive function in aging populations. Among the five cross-sectional studies, one found that subjects with low intake of thiamine, vitamins B2, B6, and folate, but not B12, scored significantly worse on verbal memory than those with relatively high intake levels. A second study found an association between vitamin B2 intake and cognitive testing in women, but not men. No association between dietary intake of B12 and cognitive function or diagnosis of AD was found in all five cross-sectional studies.

B Vitamin Status Studies

Overall. The association between thiamine status and age-related cognitive disorders is unclear. Half the studies found no associations and half found lower levels of thiamine or thiamine derivatives in tissues of patients with AD, cognitively impairment, and PD. However, none of these studies could differentiate between cause and effect (e.g., low thiamine levels resulting in disease vs. changes due to disease, including nutritional intake, resulting in low thiamine levels). The studies also failed to adjust for potential confounders. The cross-sectional studies of vitamin B2 found no association with diagnosis of AD, but low levels among people with PD (mean 101 ng/mL, where the normal range is 125 to 300 ng/mL). The large majority of vitamin B6 studies found no association between B6 status and the diagnosis of dementia or cognitive impairment, or cognitive function. A large number of studies have evaluated both vitamin B12 and folate status. Most of the longitudinal studies of vitamin B12 failed to find an association with diagnosis or severity of disease. While trends toward lower B12 levels among people with AD were found in cross-sectional studies, these associations were not consistent and proper adjustment for potential confounders was rarely performed. Both the longitudinal and case-control studies of folate status mostly reported an association between low folate levels (defined differently in different studies) and future diagnosis of AD and/or cognitive impairment. No association with PD was found.

Berries

One human study and 18 animal or in vitro studies (with 19 experiments) were evaluated.

Constituents of Berries. Only a limited number of the numerous constituents in berries have been examined separately from the rest of the fruit. These include tannins (procyanidin and prodelphinidin), anthocyanins and phenolics, from various berries.

Mechanisms of Action

Effects of the constituents in berries. One study showed that bilberry extract containing anthocyanins significantly increased rat brain uptake of triiodothyronine (T3). One study

reported that 18 plant tannins, including those found in blueberry, red currant, and gooseberry, generally inhibit brain protein kinase C to a similar degree; however, the biological significance in live animals of this in vitro inhibition is unknown. One study demonstrated that that the anthocyanins in blueberry extracts were able to cross the blood brain barrier and the number of the total anthocyanins measured in the brain is associated with rats' learning performance. One study compared the effects of specific berry constituents on neurocognitive outcomes in rats. It did not appear that the anthocyanin component was solely responsible for improvements seen.

Effects of berry extract supplementation. Berry extracts were used to supplement animals' diet or added to in vitro study media in 14 studies with 15 experiments. Of these, only two studies used specific animal or in vitro models of AD. All of these studies were from the same group of investigators.

Blueberry and strawberry extract supplementation showed improved or protective effects on almost all biochemical markers and histology findings examined in the normal-aging rat brain, although only some of the neurocognitive tests and psychomotor functions were significantly improved.

Two studies used models of AD. The results suggested that it may be possible to reduce both the deleterious effects of dopamine and the putative toxic effects of amyloid β via various berry extracts. In mouse models with amyloid precursor protein and presenilin-1 mutations, blueberry extract supplementation seemed to prevent the deficits in Y-maze performance seen in the transgenic animals fed the control diets, although it did not affect amyloid β deposits.

Human Studies. Only one study evaluated any association between berry (or berry constituent) intake and neurocognitive function. A case-control study of patients with PD found that the preference to consume blueberries or strawberries was not statistically significantly associated with PD.

Adverse Events

Only 10 B vitamin studies reported adverse events among 254 subjects receiving B vitamin supplementation. These mostly reported no adverse events. The two studies reporting complaints cited mild gastrointestinal complaints in patients with AD taking high dose thiamine and possible mild neurological complaints with folate in patients with PD.

Limitations

Animal and In Vitro Studies

Few studies used specific, well-established models for AD or PD. Most were performed in normally aging rodents. It has also not yet to be established that the neurocognitive tests used in the experiments correspond to deficits seen in AD or PD. Most studies used models of severely vitamin deficient rodents. While these studies might elucidate which B vitamins are required for maintenance of brain function, they rarely addressed the question of the actual mechanism of action of the B vitamins. Almost all the studies of berries have been performed in a single laboratory. The grading of quality for animal and in vitro studies remains even less well

validated than grading of human studies; however, improvements are clearly needed in the design and reporting of these studies.

Human Studies

Only a single, retrospective, human study of berries and PD has been reported. Among the human B vitamin studies, the majority were of poor quality. The majority of data come from cross-sectional studies, most of which failed to adjust for potential confounders. Among the trials of B vitamin supplementation, a large number were not RCTs.

All the B vitamin studies as a group also suffered from lack of standardization of B vitamin measurement technique, of normal ranges for B vitamins, of definitions of diagnoses of various dementias, and of tests of cognitive function. On the order of 50 different tests or subtests were used across the studies. There is scant evidence regarding the effect of B vitamins on PD.

Conclusions

The current research is largely inadequate to confidently assess the associations between B vitamin status and either disease or severity of disease, the effectiveness of B vitamin supplementation to prevent or ameliorate AD or PD, or putative mechanisms of action of B vitamins on age-related neurocognitive disorders.

In animal models, B vitamin deficiencies cause reproducible deficits and lesions and there is evidence to suggest a role for folate and vitamin B12 in regulating some genes and gene products related to AD.

There is limited evidence that injected vitamin B12 supplementation is of clinical benefit among demented or cognitively impaired patients, particularly when given soon after diagnosis of disease; however, overall the studies of B12 supplementation are inconclusive and the relative value of injected versus oral B12 remains unclear. Similarly, folate supplementation may also improve cognitive function but the clinical importance of the results remains unclear. Of note, though one study of folate supplementation found a significant worsening of cognitive function in treated patients with dementia. Other B vitamin treatments, including combination treatments, have not been shown to affect AD. Insufficient studies evaluated PD and no study evaluated vitamin B2 supplementation. The available literature does not conclusively support associations of B vitamin status as having an effect on age-related neurocognitive disorders. Conclusions are limited largely due to the poor quality of the research.

Almost all studies of berries and neurocognitive function have been performed by a single group of researchers. The large majority of studies have used blueberry and strawberry extract supplementation, both of which produced positive effects on biochemical markers and histology findings, and some neurocognitive tests and psychomotor functions. In studies of specific rodent models of AD, various berry extracts ameliorated the deleterious effects of the AD-related genetic defects. The human data are insufficient to make conclusions.

Future Research

Animal and In Vitro Studies

To clarify the actual biological or physiological responses that B vitamins may have on processes specific to age-related neurocognitive function, particularly PD, further studies would be needed. Studies in this field should be performed in a manner that will allow reproducibility, cross-species validation, and clear association with human brain processes. Likewise, understanding of what are the specific constituents in berries that appear to be of benefit, would require further investigation. Several questions of interest will continue to be difficult to address from human studies given ethical and practical limitations. Topics of particular interest that may be more suitable to animal research include sorting out the independent effects of elevated homocysteine and of low B vitamin levels and/or intake, and clarifying the relative harm of B vitamin deficiency (or benefit of B vitamin supplementation) in different stages of health or neurocognitive disease. Several large observational studies in humans have attempted to address the interaction with homocysteine, however, without the ability to closely control homocysteine and B vitamin levels (or intake) it is unlikely that human studies will definitively answer this question.

Human Studies

Due to either the limited amount of available data or the poor quality of the bulk of the research to date, well-performed, well-analyzed, large, prospective studies would be needed to address all the questions posed regarding the effects and associations between either B vitamins or berries and age-related neurocognitive function. Future studies should use only well-verified and commonly used measurement criteria for both predictors and outcomes. This may require additional research to verify the value of measurement tools for neurocognitive function. Further cross-sectional studies are of very limited value. Any human studies of both B vitamins and berries should be more of practical than theoretical value. For example, both dietary and supplementation studies should evaluate doses that a normal person can both easily incorporate into their lifestyle and afford, instead of testing regimens that could not be reasonably followed by most people.

EVIDENCE REPORT

Chapter 1. Introduction

The report on B Vitamins and Berries and Age-Related Neurodegenerative Disorders consists of 2 separate, but related, systematic reviews. Although sharing the same outcomes of interest, research on the effects of B vitamins and on the effects of berries do not overlap. However, given the shared outcomes of interest and the small amount of literature on berries research, this report covers both topics. The report is structured such that each chapter includes separate sections for information regarding both topics, for the B vitamin topic, and for the berries topic. In particular, the Results chapter is divided into 2 sections, one each for the B vitamin topic and the berries topic.

We begin with a general overview of age-related neurodegenerative disorders, followed by information on B vitamins and their proposed mechanisms of actions on age-related neurodegenerative disorders, and subsequently a brief introduction to berries and their proposed mechanisms of action. A detailed discussion about berry constituents is reserved for the Results chapter in response to the first berry Key Question.

Overview of Age-Related Neurodegenerative Disorders

Disorders of the nervous system account for more long-term care, chronic suffering, and lost quality of life than all other disorders combined.[1] Age-related neurodegenerative disorders are chronic and progressive conditions that result from loss of the maintenance of neurons involved in cognitive, emotional, motor and sensory functions.[2] Different neurological disorders are associated with different patterns of cell loss and different intra- or extracellular deficiencies (such as changes in the intracellular signal transduction pathways and intercellular signal molecules) or deposits in the brain. The two most common age-related neurodegenerative disorders are Alzheimer's and Parkinson's diseases.

Alzheimer's disease (AD) affects over 4 million people in the United States.[2] It is the cause of about two-thirds of all cases of dementia.[3] The prevalence of AD rises exponentially with age among the elderly such that up to half of 95 year olds are affected.[4] AD is a progressive neurological disease that results in the irreversible loss of brain neurons. It results in progressive impairment in memory, judgment, decision making, orientation to physical surroundings and language. Definitive diagnosis can be made only at autopsy, where the pathological hallmarks are neuronal loss, amyloid β-peptide plaques, and neurofibrillary tangles (or tau proteins). Human, animal model, and in vitro studies of AD generally focus on cognitive and language function or changes related to the pathological hallmarks.

The major dementia syndromes include AD, vascular disease, Lewy body dementia, Parkinson's disease with dementia, frontotemporal dementias, and reversible dementias. The most common form of dementia among elderly is AD followed by the vascular dementia. AD has one or more of the following clinical features: a decrease in the level of cognition, behavioral disturbance, and interference to activities of daily living and independence. The most frequent clinical symptom is impairment in short and long-term memory. AD is synonymously known as dementia of Alzheimer disease, presenile and senile dementia, senile dementia of Alzheimer type, etc. AD is also categorized as type 1, type 2, type 3, and type 4 based on the age of onset, familial inheritance, genetic mutation, severity of disease and the rate progression.

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) includes criteria for diagnosis of AD that has an 80% positive predictive value.[5] The Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) also includes criteria for diagnosis of AD. The diagnosis of AD in a clinical setting involves careful history preferably from the caretaker or family of the patient, assessment of cognitive function, physical and neurological examination, and laboratory and imaging work-up of the patient. The most frequently used test to assess neurocognitive function is the Mini-Mental Examination (MMSE). Extensive evaluation of the multiple domains of the cognitive function can also be done using a battery of neuropsychological tests such as Dementia Rating Scale (DRS), the Wechsler Adult Intelligence Scale-Revised (WAIS-R), among others.

Parkinson's disease (PD) affects over 1 million people in North America,[6] making it the second most common neurodegenerative disease.[3] The prevalence of PD also rises with age, but at a much lower rate than AD; approximately 0.5 to 1 percent of 65 to 69 year olds are affected, rising to 1 to 3 percent among those 80 years and older.[7] PD is characterized by resting tremor, bradykinesia (a decrease in spontaneity and movement), rigidity, and postural instability. Brain pathology is seen due to the loss of neurons in the substantia nigra in association with proteinaceous deposits known as Lewy bodies. Human, animal model, and in vitro studies of PD generally focus on related motor and neurological function or changes related to the pathological hallmarks.

A large number of other conditions result from progressive loss of neurons or neuronal function in various parts of the brain or due to numerous factors.[8] These include mild "benign" motor and cognitive changes common among aging individuals and hundreds of rarely studied specific syndromes with heterogeneous clinical and pathological expressions.

Based on a recent review article, pharmacotherapy of AD and other dementias can only provide modest cognitive or disease-modifying benefits.[9] However, even modest benefits may have significant effects on quality of life, caregiver burden, and societal economic costs. The principle recommended initial treatment for patients with AD is a cholinesterase inhibitor, regardless of severity illness. Other interventions are commonly tried, although none is recommended, primarily due to lack of evidence of a benefit. These include, among other treatments, hormone replacement therapy, anti-inflammatory treatments, gingko biloba, and various vitamin supplementations.

Basic science research has established the important role of genetics in both AD and PD. For AD, hypotheses have been proposed that mutations in precursor proteins and genes are associated with increased cellular production of products that are toxic to neurons. The first gene linked to familial AD is located on chromosome 21 and encodes the β-amyloid precursor protein (APP), the source of the 40 to 42 amino acid amyloid β-peptide that forms insoluble amyloid plaques in the brain of all AD patients. Two other genes linked to early-onset familial AD are those encoding presenilin-1 (PS1, on chromosome 14) and presenilin-2 (PS2, on chromosome 1).[10] For PD, the alpha-synuclein gene (SNCA) has been implicated in autosomal dominant forms of the disease.[11] There is a dosage effect according to the number of supernumerary copies of this gene (the number of gene duplications exceeding normal) in familial PD.[12] Other factors that have been implicated in neuronal degeneration are mitochondrial dysfunction, oxidative stress, deficient neurotrophic support, and immune mechanisms.[6]

Although the mechanisms responsible for the neuronal degeneration seen during both normal aging and neurodegenerative disease states are not fully understood, the degeneration is thought

to be caused by increased vulnerability to metabolic and extra-metabolic sources of free radicals in aging brains.[13-17] An example of the possible role of oxidative stress in dementia is suggested by a recent study that found an increased plasma homocysteine level to be an independent risk factor for the development of dementia and AD in 1,092 participants (mean age, 77 years) from the Framingham cohort with a median follow-up of 8 years.[18] With the variety of different possible pathogenic mechanisms in neuronal damage, development of therapies for these age-related neurodegenerative diseases will depend on further advances in our basic understanding of the underlying disease mechanisms. Such knowledge can potentially help in identifying high-risk individuals and lead to the development of therapies capable of halting the progression of the disorders before irreversible damage occurs.

Proposed Mechanisms of the Effect of B Vitamins on Age-Related Neurodegenerative Disorders

Here and throughout the report, we focus of the specific B vitamins B1 (thiamine), B2 (riboflavin), B6 (primarily pyridoxine), B12 (cobalamin), and folate (folic acid, tetrahydrofolate, etc.). Thiamine and riboflavin exist in a variety of food sources, including enriched and whole-grain cereals, organ meats, milk, and various vegetables. A balanced diet is generally sufficient for adequate intake of these vitamins. Dietary vitamin B6 and B12 generally come from animal protein foods (including meat, poultry, seafood, and eggs) and enriched cereals, and the major food sources of folate include green vegetables, citrus fruits, various whole grains, and, recently folate-enriched flour.

Thiamine and riboflavin, along with niacin, function in various biochemical pathways in the metabolism of glucose, amino acids, and fatty acids.[19] Thiamine deficiency, particularly associated with alcohol abuse, can result in Wernicke-Korsakoff syndrome, a distinct condition including dementia and psychosis resulting from lesions and thinning in multiple areas of the brain. There is increasing research in high-dose thiamine or riboflavin treatments in patients with AD and PD, even though the underlying mechanisms of action are unknown.[20] A recent Cochrane systematic review of the efficacy of thiamine for people with AD was inconclusive due to the small number of randomized controlled trials and poor reporting of results in the included trials.[21] The most common clinical manifestations reported in humans during vitamin B6 deficiency have been central nervous system changes and abnormal electroencephalography (EEG). Studies have showed that only 2 to 4 weeks of B6-depletion diet could result in abnormal EEG tracing in healthy young adults.[22,23]

The coenzymes of vitamin B12, folate, and vitamin B6 (methylcobalamine, methyl tetrahydrofolate and pyridoxal-5'-phosphate, respectively), along with choline, interact to control serum homocysteine levels.[19] Increased levels of homocysteine, a metabolite of the amino acid methionine, as well as decreased folate and vitamin B12 levels have been associated with normal aging. Correlations between high serum concentrations of homocysteine (in conjunction with low folate, vitamin B6 and vitamin B12) and decreased performance on cognitive tests have been reported.[24,25]

Older adults are at risk of vitamin B12 deficiency because its absorption may decline with aging. Vitamin B12 is necessary for folate metabolism. Methionine synthase, a vitamin B12-dependent enzyme, facilitates the conversion of 5-methyltetahydrofolate to tetrahydrofolate by converting homocysteine to methionine. Derivatives of tetrahydrofolate are important for

nucleotide biosynthesis. When deficiency of vitamin B12, dietary folate would stay methyltetrahydrofolate form in the body. The "methyltetrahydrofolate trap" phenomenon breaks the cycle of folate metabolism Folate acts as a cofactor in many biochemical reactions by donating and accepting one-carbon units.[11] It is essential in nucleic acid synthesis and methylation reactions in the central nervous system. Animal and cell culture models of neurodegenerative disorders have shown that low-folate/high-homocysteine diets or folate deficiency may render neurons vulnerable to dysfunction and death. Specifically, dietary folate deficiency and elevated homocysteine levels were showed to promote accumulation of DNA damage and sensitizes neurons to amyloid β-peptide toxicity in experimental models of AD, and to endanger dopaminergic neurons in experimental models of PD.[26,27] Also important to the evaluation of folate supplementation to prevent or treat neurodegenerative disorders is that excess folate intake can mask a vitamin B12 deficiency.[19]

Recommended Daily Allowances (RDA), Upper Limits (UL), and selected food sources of the B vitamins, as compiled by the Institute of Medicine (IOM) are presented in Table 1.

Overall, the B vitamins are known to function in several anti-oxidant, anti-inflammatory mechanisms, along with nucleotide biosynthesis and nerve function. However, a complete understanding of the underlying mechanisms and the relationship between B vitamins and neurodegenerative disorders, however, is still lacking.

Table 1. Institute of Medicine Dietary Reference Intakes of B vitamins, functions, and sources

Nutrient	Function	Life Stage Group	RDA	UL[a]	Selected Food Sources
Thiamine	Coenzyme in the metabolism of carbohydrates and branched chain amino acids	**Males**	(mg/d)		Enriched, fortified, or whole-grain products; bread and bread products, mixed foods whose main ingredient is grain, and ready-to eat cereals
		≥31 yr	1.2	nd	
		Females			
		≥31 yr	1.1	nd	
Riboflavin	Coenzyme in numerous oxidation/reduction reactions	**Males**	(mg/d)		Organ meats, milk, bread products and fortified cereals
		≥31 yr	1.3	nd	
		Females			
		≥31 yr	1.1	nd	
Vitamin B6 Comprises a group of 3 vitamers: pyridoxal, pyridoxine, pyridoxamine; and 5'-phosphate coenzymes of each vitamer	Coenzyme in the metabolism of amino acids, glycogen and sphingolipid bases	**Males**	(mg/d)		Fortified cereals, organ meats, fortified soy-based meat substitutes
		31-50 yr	1.3	100	
		≥50 yr	1.7	100	
		Females			
		31-50 yr	1.3	100	
		≥50 yr	1.5	100	
Vitamin B12 Including its coenzymes methylcobalamin and adenosylcobalamin	Coenzyme in amino acid and organic acid metabolism; prevents megaloblastic anemia	**Males**	(µg/d)		Fortified cereals, meat, fish, poultry
		≥31 yr	2.4	nd	
		Females			
		≥31 yr	2.4	nd	
Folate Note: Given as dietary folate equivalents (DFE). 1 DFE = 1 µg food folate = 0.6 µg of folic acid from fortified food or as a supplement consumed with food.	Coenzyme in the metabolism of nucleic and amino acids; prevents megaloblastic anemia	**Males**	(µg/d)		Enriched cereal grains, grain products, and bread products; dark leafy vegetables
		≥31 yr	400	1000	
		Females			
		≥31 yr	400	1000	

Derived from Institute of Medicine report accessed at www.iom.edu/Object.File/Master/7/296/0.pdf via www.nal.usda.gov/fnic/etext/000105.html (accessed July 27, 2005).
RDA = Recommended Daily Allowance; UL = Upper Limit.

[a] UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for thiamin, riboflavin, or vitamin B12. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

Proposed Mechanisms of the Effect of Constituents in Berries on Age-Related Neurodegenerative Disorders

There is convincing epidemiological evidence suggesting that eating fruits and vegetables may reduce the risk of cardiovascular disease and many cancers.[28] It has been hypothesized that these potential health benefits are due in part to the presence of antioxidant compounds in these foods. These beneficial compounds, such as carotenoids, vitamin C, vitamin E, polyphenols, and selenium, have been grouped together as dietary antioxidants. However, despite this grouping, these compounds can differ considerably from each another. Other non-antioxidant nutrients in fruits and vegetables, such as fiber, potassium and folate, have also been associated with several beneficial health effects.[28] The discussion of primary constituents in berries being considered regarding an effect on neurocognitive function is in the Results chapter, in response to the berries Key Question 1 regarding this topic.

Briefly, there is considerable research demonstrating the increased susceptibility of the aging brain to both oxidative stress and inflammation.[29] Data from animal and in vitro studies suggests that among the many sources of antioxidants, phytochemicals (flavonoids, phenolic acids and terpenes, derived from plants) have a beneficial role with respect to brain aging and neurodegenerative disorders through the combination of their anti-oxidative, anti-inflammatory, anti-viral, anti-proliferative, and anti-carcinogenic properties.[30] Since oxidative stress and inflammation appear to be involved in brain aging and in neurodegenerative disease states,[29] it is theorized that increased consumption of antioxidants may be effective in preventing or ameliorating these changes.

Chapter 2. Methods

Overview

This evidence report on B vitamins and berries and age-related neurodegenerative disorders is based on a systematic review of the literature. The Tufts-New England Medical Center Evidence-based Practice Center (Tufts-NEMC EPC) held meetings and teleconferences with a technical expert panel (TEP) to identify specific issues central to this report. The TEP was comprised of technical experts in basic and clinical research in neuroscience, nutrition, B vitamins, and berries. A comprehensive search of the medical literature was conducted to identify studies addressing the key questions. Evidence tables of study characteristics and results were compiled, and the methodological quality and the applicability of studies were appraised. Study results were summarized with both qualitative and quantitative reviews of the evidence, evidence and summary tables

A number of individuals and groups supported the Tufts-NEMC EPC in preparing this report. The TEP served as our science partner. It included technical experts, representatives from the Agency for Healthcare Research and Quality (AHRQ), and both the National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Dietary Supplements (ODS) at the National Institutes of Health (NIH). The TEP worked with the EPC staff to refine key questions, identify important issues, and define parameters for the report. Additional clinical domain expertise was obtained through local experts who joined the EPC. A draft version of this report was critically appraised by a panel of peer reviewers.* Revisions were made based on their comments; although all statements within the report are those of the authors only.

The review process and the report have been structured to account for the separate, but parallel, issues related to the effects of B vitamins and of berries. Processes related to neuroscience and to understanding animal and in vitro studies occurred in conjunction with all team members and relevant TEP members, whereas those related to either B vitamins or berries specifically occurred separately. Because of the small amount of literature related to berries and neurocognitive outcomes, the report encompasses both interventions. The report Introduction, Results, and Discussion chapters are structured such that common issues and topics are discussed first, followed by B vitamins, and then berries.

Key Questions Addressed in This Report

B Vitamins

1. What is the evidence regarding mechanisms of action of the B vitamins B1, B2, B6, B12, and folate (singly and in combination) for preventing, decreasing the rate of progression of, or reversing the neurological changes associated with age-related neurodegenerative conditions such as Parkinson's or Alzheimer's disease?

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/berry/berry.pdf.

2. What is the evidence that the B vitamins B1, B2, B6, B12, and folate can prevent, decrease the rate of progression of, or reverse the neurological changes associated with age-related neurodegenerative conditions such as Parkinson's or Alzheimer's disease in humans

3. What adverse events in humans have been reported in the literature for supplementation with the B vitamins B1, B2, B6, B12, and folate?
    a. Do the frequency of adverse events vary with source, dose, or other evaluated factors?

Berries

1. What are the constituents in berries with beneficial nerve- and brain-related health effects (from in vitro, animal, and human studies)?
    a. In what other food sources are these constituents found?

2. What is the evidence regarding mechanisms of action of berry constituents for preventing, decreasing the rate of progression of, or reversing the neurological changes associated with age-related neurodegenerative conditions, including Parkinson's or Alzheimer's disease?

3. What is the evidence that the constituents of berries can prevent, decrease the rate of progression of, or reverse the neurological changes associated with age-related neurodegenerative conditions, including Parkinson's or Alzheimer's disease in humans
    a. Is the source, species, dose, composition, characteristics, or processing of berries and berry constituents related to the effect of the intervention?

4. What adverse events in humans have been reported in the literature for the constituents in berries?
    a. Do the frequency of adverse events vary with source, dose, or other evaluated factors?

Approach To Analyzing the Literature

To guide the assessment and synthesis of the literature, we used an expanded version of the generally-referred-to "PICO" method (Population, Intervention, Comparator, Outcomes) to define the parameters of interest. We used this approach for analysis of both human, animal, and in vitro studies. With input from the TEP, we asked the following questions to establish the literature review criteria:

- What are the populations of interest?
- What are the interventions of interest?
- What are the comparators of interest?
- What are the (marker/intermediate and clinical) outcomes of interest?
- What are the health conditions of interest?
- What are acceptable study designs?

Topic Refinement

In regards to both studies that examine putative mechanisms of action on neurodegenerative disorders and to studies that examine associations and effects in humans on neurodegenerative disorders, there is a very broad range of related topics that have been studied. In an iterative process, the EPC worked with the TEP to focus the questions and the topics on those that are most likely to shed light on mechanisms of action and effects related to Alzheimer's disease (AD), Parkinson's disease (PD) and related neurocognitive disorders. Thus this report does not evaluate all mechanisms of action or all associations related to neurological function. Given the very large number of studies (both human and animal) related to B vitamins, and the small number of studies of berries, these caveats apply primarily to B vitamin topics.

The following topics were chosen, in consultation with the TEP, for evaluation:

B Vitamins: Human Studies

- Association between B vitamin treatment/intake with diagnosis of AD or PD, cognitive function, or histopathology (primary prevention of disease)
- Association between B vitamin treatment/intake with severity of AD or PD, cognitive decline, or histopathology. (secondary prevention/treatment)
- Association of B vitamin levels and AD or PD diagnosis, or histopathology
- Association of B vitamin levels and AD or PD severity
- Association of B vitamin levels and cognitive function

B Vitamins: Animal / In Vitro Studies

- Effect of B vitamin supplementation or deficiency on cognitive function, movement disorders, histopathology, L-dopa and pre-cursor levels, etc., in appropriate models
- Effect of B vitamins on the expression or function of AD-related genes (presenilin, alpha-2 macroglobulin, amyloid precursor protein, Apo E4)
- Blood brain barrier function in relation to B vitamins
- Cerebrovascular endothelial function in relation to B vitamins

Thus, the following potential topics (among others) are not reviewed: B vitamin-dependent enzyme levels or function; markers of inflammation or other potential causes of neurocognitive decline, including homocysteine, except as they relate to the association between B vitamins and neurocognitive status; B vitamin megadose-related toxicity; animal studies using B vitamin antagonists, brain lipid metabolism, animal perinatal and growth-related brain/nerve/cognition development; genes related to B vitamin function or enzymes such as MTHFR; GABA metabolism, or neuron ion channels.

Berries. Given the small size of the relevant literature, all studies evaluating the effect or association of berries or constituents of berries with any neurological or cognitive outcome were included.

Eligibility Criteria

This report encompasses evaluations of both clinical human studies and basic science studies performed in animal and in vitro models. Therefore, specific eligibility criteria were needed for

each topic. We first describe the common eligibility criteria for any study included in this report, followed by additional specific criteria for each topic.

Human Studies. The common inclusion criteria for human studies analyzed in this report consist of primary studies; English language publication, human adult subjects; analysis of the predictor or description, including quantification, of the intervention, and analysis of the following categories of outcomes: diagnosis or severity (degree) of AD, PD, other age-related neurocognitive disorder, or cognitive impairment; test of cognitive function. We excluded studies of mental retardation, including Down syndrome, Wernicke's encephalopathy, subacute combined degeneration, vascular dementia, acute encephalopathy, and mixed causes of dementia lacking separate analyses for disease types. Also excluded were studies of peripheral neuropathy and other lower motor neurodegeneration not related to PD. However, studies that compared groups of patients with age-related neurocognitive disorders with groups of patients with other dementias were included. We also excluded case reports and studies of non-applicable populations, such as young patients with diabetes. Abstracts without an associated full report were excluded. Where studies were reported in multiple publications, the more completely reported and/or the report with the longer duration of follow-up were used; although data from multiple publications of the same study may be combined.

Animal / In Vitro Studies. Animal and in vitro studies had to be published in full form, excluding abstracts, in English language journals. We included all animal and in vitro models of diseases of interest and all outcome measurements related to the outcomes and/or associations of interest. We excluded studies that used inappropriate animal or in vitro models, such as immature animals and non-neuronal cells.

B Vitamin Topics

Common criteria. The following B vitamins were investigated:

- B1 (thiamine)
- B2 (riboflavin)
- B6 (pyridoxine and related compounds)
- B12 (cyanocobalamin)
- Folate

We included evaluations of the single vitamins and combinations of the B vitamins. We excluded evaluations of "multivitamins" that included vitamins other than B vitamins. Evaluation of B vitamins could be from supplements (given by any route), food sources, or specific tissue concentrations. Evaluated body levels included blood, serum, plasma, cerebrospinal fluid, or tissue sample (including red blood cell) levels of the specific vitamins and commonly measured metabolites (i.e., pyridoxal-5'-phosphate, the active coenzyme form of B6, and thiamine pyrophosphate, the active coenzyme form of B1). We allowed any measurement methodology. We did not include other proxies for B vitamin levels (e.g., thiamine-dependent enzyme activity).

Human intervention studies (trials). We included only prospective trials of clearly defined B vitamin interventions. We allowed randomized controlled trials (RCTs), prospective non-randomized comparative trials, and prospective cohort studies (single arm studies without a control group). We allowed trials of both supplements and food sources. We excluded studies of

the effect of B6 intake on Parkinsonian symptoms and L-dopa levels in patients using L-dopa treatment. (This issue is discussed in the adverse events section of the results.)

Human association studies. Among studies that reported associations between B vitamin levels and neurocognitive outcomes, we included only those that included subjects with either AD or PD, or neurocognitive impairment, excluding studies focusing on cognitively normal populations. All studies, regardless of sample size, were included regarding PD or vitamins B1, B2, or B6 levels. For cross-sectional studies of either B12 or folate levels and subjects with either AD or cognitive impairment, we included only studies that evaluated both at least 100 subjects total and 30 subjects with AD or cognitive impairment (not including vascular dementia, mental retardation, etc.). However, we included all longitudinal studies, regardless of sample size.

For studies evaluating B vitamin intake (i.e., by food frequency questionnaires), we included only studies with at least 50 subjects. We chose this arbitrary threshold to as a minimum number of subjects required to ensure adequate power for associations to be investigated in these retrospective studies. Studies of food intake (from food frequency questionnaires) must have had comparison groups of subjects with different levels of neurocognitive function. In addition we excluded cross-sectional intake studies that examined only dietary intake of patients with dementia. These studies evaluated nutritional deficiencies caused by poor diet due to dementia, which was not considered to be of interest.

For both human intervention and association studies, we did not include evaluations of outcomes related to depression, other psychiatric conditions, sleep, appetite, or other somatic conditions. We evaluated only diagnoses or measures of cognitive function or symptoms of PD.

Animal / in vitro studies. We excluded animal or in vitro models specific to Wernicke's encephalopathy; namely models of thiamine deficiency combined with ethanol. Although, if sufficient data regarding thiamine deficiency without ethanol was also included, these studies were reviewed. We also excluded animal and in vitro models that caused or exacerbated B vitamin deficiency with B vitamin antagonists. In addition, "case reports" or "case series" of B vitamin deficiencies in farm animals were excluded.

Berry Topics

Common criteria. After reviewing various definitions of berries and in consultation with the TEP, the following berries were included:

- Bilberry
- Black raspberry
- Blackberry
- Blueberry
- Boysenberry
- Cranberry
- Currants
- Gooseberry
- Lingonberry
- Marionberry
- Raspberry
- Strawberry

We recognized that these common terms for berries do not always match one-for-one with specific species. We allowed all fruits that are commonly designated among these berries. We included studies that used whole berries or specific constituents of berries. We did not include studies that evaluated constituents found in berries that were not derived from berries (e.g., purified quercetin).

Human studies. We included any study that examined the effect of or association between berries and any neurocognitive outcome in any population.

Animal / in vitro studies. We exclude studies using amphetamine- or lithium chloride-induced conditioned taste avoidance (CTA) as rats' learning or behavioral outcome. The CTA paradigm measures the avoidance by rats of a sucrose solution that has been paired with a high dose of a drug, such as amphetamine. The LiCl is used as a control. "Learned safety" theory is the mechanism of CTA results;[31] it is not related to age-related cognitive or behavioral function.

Other Topics

Constituents in berries. Regarding the berry Key Question 1 on the constituents in berries related to neurological effects, we evaluated introduction and discussion sections from articles reviewed for other berry topics and also searched for both systematic and general reviews of the topic.

Adverse events. For both B vitamins and berries we included any adverse event data from otherwise evaluated human studies. We also reviewed other human studies that did not meet criteria for inclusion for other topics. In addition, we searched for both systematic and general reviews regarding adverse events in humans. We included all systematic reviews. General reviews were included on an ad hoc basis, depending on generalizability and adequacy of source material. We excluded adverse events related to pregnancy, children, contraception, cancer, and specific drug interactions (methotrexate, colon cancer chemotherapy, etc.). For berries, we also excluded allergies and issues related to food contaminants.

Literature Search Strategy

We conducted a comprehensive literature search to address the key questions.* Final literature searches for English language publications on B vitamins were conducted in MEDLINE® and the Commonwealth Agricultural Bureau (CAB) Abstracts™ on February 2, 2005 and for berries, in the same databases, on March 3, 2005. Search terms included subject headings and textwords with filters to limit the publications to English language. Subject headings and text words were selected so that the same set could be applied to both databases. The searches included both human, animal, and in vitro studies. Among the articles in MEDLINE®, specific article types were excluded, such as editorials, letters, and case reports, and other types that would not meet eligibility criteria.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/berry/berry.pdf.

Both the B vitamin and berry searches used a common neurocognitive model that included the following terms: nervous system diseases, cognitive disorders, neurodegeneration, dementia, Alzheimer, Parkinson, Lewy body, neuron/nerve cells, brain, and related terms.

The B vitamin search included both common and chemical names for all the B vitamins of interest. The berry search included both common and botanical names for all the berries of interest and the term "fruit," excluding "fruit fly." In addition, we included a list of 33 chemical terms for known berry constituents.

Additional studies were sought by contacting members of the TEP, and from reference lists of selected included articles and review articles and meta-analyses. Although the large majority of evidence regarding berries was from a single group of investigators, the decision was made with the TEP to maintain the restriction of eligible literature to published, peer-reviewed articles.

Study Selection and Data Extraction

All citations identified through the literature search were screened according to the inclusion criteria. A low threshold for acceptance was used at this stage to maximize the retrieval of potentially useful studies. Retrieved articles were evaluated against the complete inclusion criteria.

A single reviewer extracted each eligible study.[*] Data extraction problems were addressed during weekly meetings. Occasional sections were re-extracted to ensure that uniform definitions were applied across extracted studies. Problems and corrections were noted through spot checks of extracted data and during the creation of summary and evidence tables. A second reviewer independently verified the data in the summary tables using the original article.

Data Extraction

The same data extraction forms were used for both the B vitamin and berry articles.

Human Studies. Two data extraction forms were created for human studies; one for interventions, and one for associations. These forms were designed in the format of an evidence table to allow simple conversion to these tables. In both forms, items extracted included: factors related to study characteristics (study design, duration, country, setting, funding source), population (age, sex, race), eligibility criteria, definitions of neurocognitive disorders, study sample (number enrolled, number analyzed, reasons for dropout), descriptions of interventions or predictors and of outcomes, limitations, comments, and an assessment of both study quality and applicability (see below).

Intervention forms also captured results data related to baseline, follow-up, change, and net change in outcomes, along with standard deviation or standard error and statistical significance. Association forms captured results data related to mean outcome values of different groups, correlation values (r, odds ratio, relative risk, hazard ratio, etc.), and statistical significance of either differences or associations.

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/berry/berry.pdf.

Animal and In Vitro Studies. Animal and in vitro studies are usually designed to examine the proposed mechanisms or pathways for the observed effects of a substance on defined diseases or conditions in humans. These studies are generally not meant to provide precise estimates of effects, but instead to test alternative hypotheses. Therefore, the process in reviewing animal and in vitro studies is different than reviewing human clinical or epidemiological studies. In contrast to traditional systematic reviews of human studies where large heterogeneity across studies related to different models and outcomes being examined can be problematic, in basic science studies heterogeneity (such as different models) across studies is essential to test and eliminate alternative hypotheses (such as different outcomes), so long as the central hypothesis (e.g., the physiological application) is related.

Thus, the goal of data extraction for these articles was not to extract the exact quantitative findings of each study. Instead, we extracted the following information to capture the concepts of importance. Namely,

- What is the central hypothesis or stated purpose of the study?
- What is the authors' assessment of the gap between what is known and unknown?
- What is the working model used in the study?
- What is the study design (including characteristics, intervention, comparator, and outcomes, sample size, duration)?
- What are the measurements or outcomes?
- What are the results and authors' conclusions?
- What is the quality (including limitations) of the study?

Grading of the Evidence

Studies accepted in evidence reports have been designed, conducted, analyzed, and reported with varying degrees of methodological rigor and completeness. Deficiencies in any of these components can lead to biased reporting and interpretation of the results. While it is desirable to grade individual studies to highlight the degree of potential bias, the grading of study quality is a challenging process. Most factors commonly used in quality assessment of RCTs do not demonstrate a consistent relationship to estimates of treatment effects.[32] Thus, there is still no uniform approach to grade studies. For human studies of both B vitamins and berries, our EPC has adopted the following approach, as used in previous evidence reports.

Methodological Quality Grade (Human Studies)

We used a 3-category grading system (A, B, C) to denote the methodological quality of each study. This grading system has been used in most of the previous evidence reports from the Tufts-NEMC EPC as well as in evidence-based clinical practice guidelines.[33] This system defines a generic grading system that is applicable to varying study designs including RCTs, non-randomized comparative trials, cohort, and case-control studies:

A Category A studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: clear description of the population, setting, interventions and comparison groups; sufficient power (arbitrarily defined as minimum sample size of 10 subjects); clear

description of the content of the intervention or predictor used; appropriate comparator; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20% dropout; clear reporting of dropouts; and no obvious bias. Intervention trials must be double-blinded RCTs. Correlation analyses must use prospectively gathered data and must perform appropriate adjustment for potential confounders.

B Category B studies are susceptible to some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category A because they have some deficiencies, but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

C Category C studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis or reporting, have large amounts of missing information, or discrepancies in reporting. Specific criteria included large (>20%) or unequal dropout rate, large discrepancy in baseline and final numbers of subjects, non-randomized or single-cohort intervention studies, dissimilar baseline values among cohorts, unclear duration or numbers of subjects, missing baseline data, or irreconcilable apparent differences between data in figures, tables, and text.
In addition, cross-sectional association studies (between vitamin B level and either diagnosis or cognitive test score) that did not adjust for any potential confounders (i.e., performed only univariate analyses without relevant sub-analyses).

Methodological quality scoring was performed near the end of the review when we had the most experience and knowledge about the included studies. Each included study was graded by at least 2 people (with the exception of studies with major deficiencies, such as a non-comparative study design). When there were disagreements, 1 or 2 additional reviewers graded the studies and consensus was reached. Approximately half the studies had quality scoring by 3 or more reviewers.

Methodological Quality Grade (Animal / In Vitro Studies)

Although we used the same 3-category grading system (A, B, C) to denote the methodological quality of each study, the criteria used to assess the methodological quality of animal or in vitro studies are different from those used for human studies. Compared to human clinical trials, randomization of treatments and blinded analysis may be essential, but is often not applicable to animal or in vitro experiments. Therefore, we did not incorporate these factors into our quality grading system. This system defines a generic grading system that is applicable to both animal and in vitro studies:

A Category A studies have the least bias and results are considered valid. A study should report comprehensive background information on animals or cell lines used. For animals, the information should include the animal source, strain, sex, age, body weight, housing condition (diet, light/dark cycle, number of animals per cage), and experimental environment (ambient temperature, time of day, and season). For cell lines, the information should include the origin, growth media, and experimental environment. The

number of animals in the experiments and animals excluded from a study, and the reasons for their exclusion, must be reported. Controls should be contemporary and preferably be approximately equal in group size to the intervention groups. Treatments (e.g., the compositions of experimental and control diets) and outcome measures should be clearly defined and reported. Experimental models should be independent of each other. All experiments should have at least one repetition.

B Category B studies are susceptible to some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category A because they have some deficiencies, but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

C Category C studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis or reporting, have large amounts of missing information, discrepancies in reporting or irreconcilable apparent differences between data in figures, tables, and text.

Applicability Grade

Only human studies were assessed for applicability. For animal and in vitro studies, no assessment was made as to the applicability of the experimental model.

Applicability addresses the relevance of a given study to a population of interest. Every study applies certain eligibility criteria when selecting study subjects. Most of these criteria are explicitly stated (e.g., disease status, age, sex). Some may be implicit or due to unintentional biases, such as those related to study country, location (e.g., community vs. specialty clinic), or factors resulting in study withdrawals. The question of whether a study is applicable to a population of interest (such as Americans) is distinct from the question of the study's methodological quality. For example, due to differences in the background diets, an excellent study of Japanese men may be very applicable to people in Japan, but less applicable to Japanese American men, and even less applicable to African American men. The applicability of a study is thus dictated by the questions and populations that are of interest to those analyzing the studies.

In this report, the focus is on individuals at increased risk for, or diagnosed with, age-related neurocognitive disorders; in particular AD or PD. Even though a study may focus on a specific target population, limited study size, eligibility criteria, and the patient recruitment process may result in a narrow population sample that is of limited applicability, even to the target population. To address this issue, we categorized studies within a target population into 1 of 3 levels of applicability that are defined as follows:

 Sample is representative of the target population. It should be sufficiently large to cover both sexes, an appropriate age range, and other important features of the target population (e.g., general health status). At least 30 subjects analyzed.

 Sample is representative of a relevant sub-group of the target population, but not the entire population. Limitations include such factors as narrow age range, single

ethnicity, setting that applies to only a portion of the population (e.g., nursing home). At least 10 subjects analyzed.

- Sample is representative of a narrow subgroup of subjects only, and is of limited applicability to other subgroups. For example, a study of the oldest-old men or a study of a population on a highly controlled diet.

Reporting Results

Outcomes Reported

For both human intervention studies and animal / in vitro studies we evaluated all outcomes relevant to neurocognitive function that were reported in studies. However, for human association studies regarding cognitive function, in consultation with the TEP, we focused the detailed evaluation to a limited number of outcomes. A large number of tests of cognitive function have been used by different study groups. Few of these have been validated in any systematic way. Interpretation of tests used by single groups or that have not been validated can be problematic. Thus we evaluated in detail the following tests of cognitive function:

- Mini-mental status examination (MMSE) and modifications
- Alzheimer's Dementia Assessment Scale (ADAS)
- Mattis' Dementia Rating Scale (DRS)
- Wechsler Adult Intelligence Scale (WAIS)

Other cognitive tests are summarized qualitatively only. All relevant outcomes in studies of patients with PD are reported in detail, as are all associations between B vitamin levels and diagnoses of cognitive disorders.

Metrics Included

Human Intervention Trials. For controlled intervention trials the summary tables describe 3 sets of data: the mean baseline levels in both intervention and control arms, within-cohort changes (e.g., $\text{Intervention}_{\text{Final}} - \text{Intervention}_{\text{Initial}}$), the net change of the outcome, and the reported *P* values of both the within-cohort change and the net change. The net change of the outcome is the difference between the change in the intervention arm and the change in the control arm:

$$\text{Net change} = (\text{Intervention}_{\text{Final}} - \text{Intervention}_{\text{Initial}}) - (\text{Control}_{\text{Final}} - \text{Control}_{\text{Initial}}).$$

For non-controlled interventions, we report the within-cohort changes and *P* values. For both types of studies we did not calculate any *P* values, but, when necessary, used provided information on the 95% confidence interval or standard error (SE) of the net difference to determine whether it was less than 0.05. We included any reported *P* value less than 0.10; those above 0.10 and those reported as "non-significant" were described as "NS" (non-significant) in the tables.

Human Association Studies. For studies reporting mean B vitamin levels, mean cognitive function scores, or prevalence of disease in different groups of patients, these values are included in summary tables along with reported *P* values of differences among the groups. For studies that reported further analyses, such as odds ratio or relative risk, or correlation (r) between, for

example, B vitamin level and cognitive test score, these values are reported, along with their statistical significance. When available, both unadjusted and adjusted values are included.

Animal / In Vitro Studies. Numerical results are not reported for the basic science studies. We aimed to capture the direction and the statistical significance of all outcomes. For each analysis we report a symbol for the effect and the statistical significance (when reported). We used the following symbols:

- **+** Normal B vitamin animals/tissue performed better than B vitamin-deficient animals/tissue, or
  Berry-fed animals/tissue performed better than non-berry-fed animals/tissue
- **0** No difference in performance
- **—** Normal B vitamin animals/tissue performed worse than B vitamin-deficient animals/tissue, or
  Berry-fed animals/tissue performed worse than non-berry-fed animals/tissue

The assessment of whether animals or tissue receiving the intervention performed better than controls was made based on a combination of the reported results, the statistical significance, and the conclusions of the authors.

Units. For measures of B vitamin levels, the original units reported in the study were included in the evidence tables. However, all such measurements were converted to standard units (e.g., mg/dL) in the summary tables to facilitate comparisons.

Evidence and Summary Tables

The evidence table offers a detailed description of the studies that addressed each of the key questions. The evidence table is available via the internet.* The tables provides all the information that was extracted from each study (as described above, under *Data extraction*). Each study appears once regardless of how many interventions or outcomes were reported. The evidence tables of human studies are ordered alphabetically by the first author, then by publication date. The evidence tables of animal and in vitro studies are categorized by topic and ordered chronologically, so as to capture the sequence of the research.

Summary tables are included in each Results section. They succinctly report summary measures of the main outcomes evaluated. They include information regarding study duration (as applicable), study size, intervention and control, outcomes, results, methodological quality, and study applicability. They are designed to facilitate comparisons and synthesis across studies. Studies reporting multiple predictors (e.g., B vitamins) may appear several times in summary tables. Blank cells indicate that the relevant data were not reported in the articles.

Studies that did not report detailed reports of interest to this report are included in the summary tables. The qualitative results – whether a significant or non-significant association – are included either as a paraphrase of or direct quote from the authors.

Within summary tables of human studies, studies were ordered first by outcome test (for cognitive tests: MMSE, ADAS, DRS, WAIS, then others), then from highest quality to lowest, then from highest applicability to lowest, then from largest to smallest number of subjects. Summary tables of animal and in vitro studies are ordered chronologically.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/berry/berry.pdf.

Adverse Events Reporting

We used the term adverse event as defined by the World Health Organization (WHO) International Conference on Harmonization. An adverse event is "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product." An adverse drug reaction is any "noxious and unintended response to a medicinal product related to any dose…" (www.fda.gov/cder/guidance/iche2a.pdf).

We reviewed all accepted and rejected human studies of either B vitamins, berries, or berry constituents being used as an intervention for data on adverse events and drug interactions. These reports included randomized trials, cohorts, case-control studies, and individual case reports and series. We excluded allergies (except for anaphylaxis) and occupational exposures.

Since adverse event reporting was very limited among the reviewed studies, we also performed searches for both systematic reviews and review articles regarding adverse events due to either B vitamins or berries. We also performed a search of articles on berries that have been tagged by MEDLINE® or CAB Abstracts™ as addressing adverse events.

Chapter 3. Results

B Vitamins

In this section, we summarize the results from human and animal or in vitro studies of the B vitamins – B1 (thiamine), B2 (riboflavin), B6 (pyridoxine and related chemicals), B12 (cobalamin), and folate – in relation to age-related neurodegenerative disorders (primarily Alzheimer's disease [AD] and Parkinson's disease [PD]). The three Key Questions to be answered are as follows:

1. What is the evidence regarding mechanisms of action of the B vitamins B1, B2, B6, B12, and folate (singly and in combination) for preventing, decreasing the rate of progression of, or reversing the neurological changes associated with age-related neurodegenerative conditions such as Parkinson's or Alzheimer's disease?

2. What is the evidence that the B vitamins B1, B2, B6, B12, and folate can prevent, decrease the rate of progression of, or reverse the neurological changes associated with age-related neurodegenerative conditions such as Parkinson's or Alzheimer's disease in humans

3. What adverse events in humans have been reported in the literature for supplementation with the B vitamins B1, B2, B6, B12, and folate?
    a. Do the frequency of adverse events vary with source, dose, or other evaluated factors?

Findings are presented in the order of the Key Questions.

The final search of MEDLINE® and CAB Abstracts™ yielded 6,640 citations. This search included human, animal, and in vitro studies. After screening of the titles and abstracts, 183 articles on human studies and 87 articles on animal or in vitro studies. An additional 15 human studies and 1 animal study were found from review articles, study reference lists, and domain experts. From these, 83 human studies and 27 animal or in vitro studies were included in this review. However, though the review covers both neurocognitive function related to AD and related diseases and the movement disorders and motor systems degeneration related to PD and related diseases, only scant evidence was found regarding PD-related conditions.

Qualifying studies are presented in summary tables in the appropriate sections. Details regarding all included studies are available in the evidence tables.*

Animal and In Vitro Studies: Mechanisms of Action

All studies related to mechanisms of action of B vitamins have been performed in animal or in vitro models. A total of 17 studies were included in this section. Of these, 10 examined the

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/berry/berry.pdf.

effects of B vitamins on animals' cognitive function, movement disorders and brain neurotransmitters or histopathology (Tables 2-5). Only one in vitro study and one animal study with three publications examined the effects of B vitamins on the expression or function of AD-related genes. Five studies examined the effects of B vitamins on the blood brain barrier (BBB) or cerebrovascular endothelial function (Table 6).

Effects of B Vitamins on Cognitive Function, Movement Disorders, and Brain Neurotransmitters or Histopathology

Study Descriptions. The effects of B vitamins on cognitive function, movement disorders and brain neurotransmitters or histopathology in animal and in vitro models were described in 10 studies in 11 publications.[26,27,34-42] Four studies in five publications used thiamine deficient models in rats. Three studies were of moderate quality, and one was of poor quality (Table 2). Two examined the effects of B6 treatments on animals' performances in neurocognitive tests. One was of high quality and the other one was of moderate quality (Table 3). One high quality study used models of vitamin B12 supplementation in rats.(Table 4). Three studies used folate deficient models alone or in combination with PD or AD models in mice or rats. Three studies were of high quality and one of moderate quality (Table 5). We found no study that examined the effects of riboflavin (vitamin B2) or mixed vitamin B treatments on outcomes of interest.

Overall Effects

Thiamine (B1). The overall findings of the effects of thiamine deficiency are summarized in Figure 1. Of the four studies (in five publications) using thiamine-deficient models, two examined the rats' clinical status and/or histopathology after 44 days or 35 weeks of thiamine-depleted diets, and three examined rats' performance in neurocognitive tests (Table 2).[34-36,38,39] The two studies that examined the rats' clinical status and/or histopathology found that a diet without thiamine significantly damaged the rats' brains and/or caused serious neurological pathology, including death. In the other two studies that examined the effects of thiamine deficiency on rats' performance in neurocognitive tests, the deficient regimens varied widely. Specifically, Terasawa 1999 fed the rats a low-thiamine diet (30 mg per 100 g diet) for approximately 42 days, and Ciccia 2000 fed the rats a vitamin-fortified chow in combination with a thrice-weekly thiamine injection (1 mg per kg body weight) for three episodes of thiamine deficiency. Each episode lasted about 4.5 weeks. Terasawa 1999 found rats fed thiamine-deficient diets had significantly impaired performances in the neurocognitive tests when compared to the control rats. Ciccia 2000 found that rats with three separate episodes of thiamine deficiency had significantly impaired performance in two of eight neurocognitive tests.

Pyridoxine (B6). Two studies used a vitamin B6-supplementation model in mice or rats and both studies examined different doses of B6 supplementation on performances in neurocognitive tests (Table 3).[41,42] No significant effects of B6 supplementation were found for rat learning or cognitive function. Dietary B6 supplementations showed some positive effect on motor function or behavior, although the effects were not consistent across the two studies. The studies did not find a linear dose-response relationship for the effects; however, the results suggested worse motor function was associated with a lower dose of dietary B6 supplementation.

Cyanocobalamin (B12). One study examined the effects of low-dose vitamin B12 supplementation on spontaneous movements and performance in the Morris Water Maze in rats

with nucleus basalis magnocellularis (NBM) lesions (an animal model that mimics some of the cholinergic hypofunction and memory loss associated with AD; Table 4).[37] The study found that low dose (1 mg per kg diet) vitamin B12 supplementation alone had no significant effect on spontaneous movements and did not improve memory in rats with NBM lesions.

Folate. Three studies examined the effects of folate deficiency on animal performance in neurocognitive tests and on brain neurotransmitters or histopathology; two used a normal animal model, one used a PD model and one used an AD model (Table 5).[26,27,40] Kim 2002 conducted a electron microscopic experiment comparing the cerebrocortical microvascular wall in brain cross sections with rats fed a diet without folate to that of rats fed a diet with folate (4 mg per kg diet). After 8 weeks of dietary treatments, a degenerative appearance of the cerebrocortical microvascular wall occurred in rats fed folate-deficient diet, while rats fed a diet with folate had a normal cerebral capillary wall. Duan 2002 tested the effects of folate deficiency using a rat model of PD. After 3 months of dietary treatments, both experiment and control animals received two intraperitoneal injections of 20 mg 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) per kilogram body weight. The MPTP toxin induced PD-like pathology and behavioral symptoms. In contrast to mice on the control diet that were resistant to the sub-toxic dose of MPTP, mice maintained on the folate-deficient diet exhibited profound motor dysfunction as indicated by a decrease in the period of time in which they were able to maintain themselves on the rotarod and by an increased number of falls. However, folate deficiency alone did not impair rats' performance on rotarod tests. Kruman 2002 examined the effects of folate deficiency on brain histology findings in amyloid precursor protein (APP) mutant mice. These mice developed age-dependent deposition of amyloid β-peptide in their brains. There was no significant difference in the levels of amyloid β deposition between APP mutant mice on the folate-deficient diet and those on the control diet. However, the analyses in the CA3 region of the hippocampus revealed a highly significant 20 percent loss of neurons in APP mutant mice on the folate-deficient diet compared with those on the control diets. These results suggested that folate deficiency renders hippocampal CA3 neurons in APP mutant mice vulnerable to death by a mechanism that does not involve increased amyloid β production or deposition.

Summary. Of the four studies that used thiamine-deficient models, two examined the rats' clinical status and/or histopathology after thiamine-depletion diets and all found that thiamine-depletion diets significantly damaged brain and/or cause serious neurological pathology, including death. The remaining two studies that examined rat performance in neurocognitive tests found that thiamine deficiency had significantly impaired performance in some neurocognitive tests.

Two studies used a B6-supplementation model in mice or rats to examine the effects of B6 treatments on performance in neurocognitive tests. Both studies that used the B6-supplementation model examined various doses of B6 supplementation on animal performance in neurocognitive tests. No significant effects of B6 supplementation were found on rats learning or cognitive function. Dietary B6 supplementations showed some positive effect on animal motor function or behavior, although the effects were not consistent across the two studies and did not show a linear dose-response relationship.

One study showed that low dose (1 mg per kg diet) vitamin B12 supplementation alone had no significant effect on spontaneous movements and did not improve memory in rats with NBM lesions.

Of the three studies that examined the effects of folate deficiency on animal performance in neurocognitive tests and brain neurotransmitters or histopathology, two used a normal animal model, one each used a PD model and an AD model. Results from the normal animal model showed a degenerative appearance of the cerebrocortical microvascular wall was shown in rats fed a folate-deficient diet for 8 weeks, but 3-month folate-deficient diet did not impair rats' performance on rotarod tests. The one study that tested the effects of folate deficiency using a rat model of PD found that mice which had been maintained on the folate-deficient diet exhibited profound motor dysfunction induced by MPTP, in contrast to mice on the control diet that were resistant to the sub-toxic dose of MPTP. The results from the one study that used an AD model to examine the effects of folate deficiency on brain histology findings in APP mutant mice suggested that folate deficiency renders hippocampal CA3 neurons in APP mutant mice vulnerable to death by a mechanism that dose not involve increased amyloid β production or deposition.

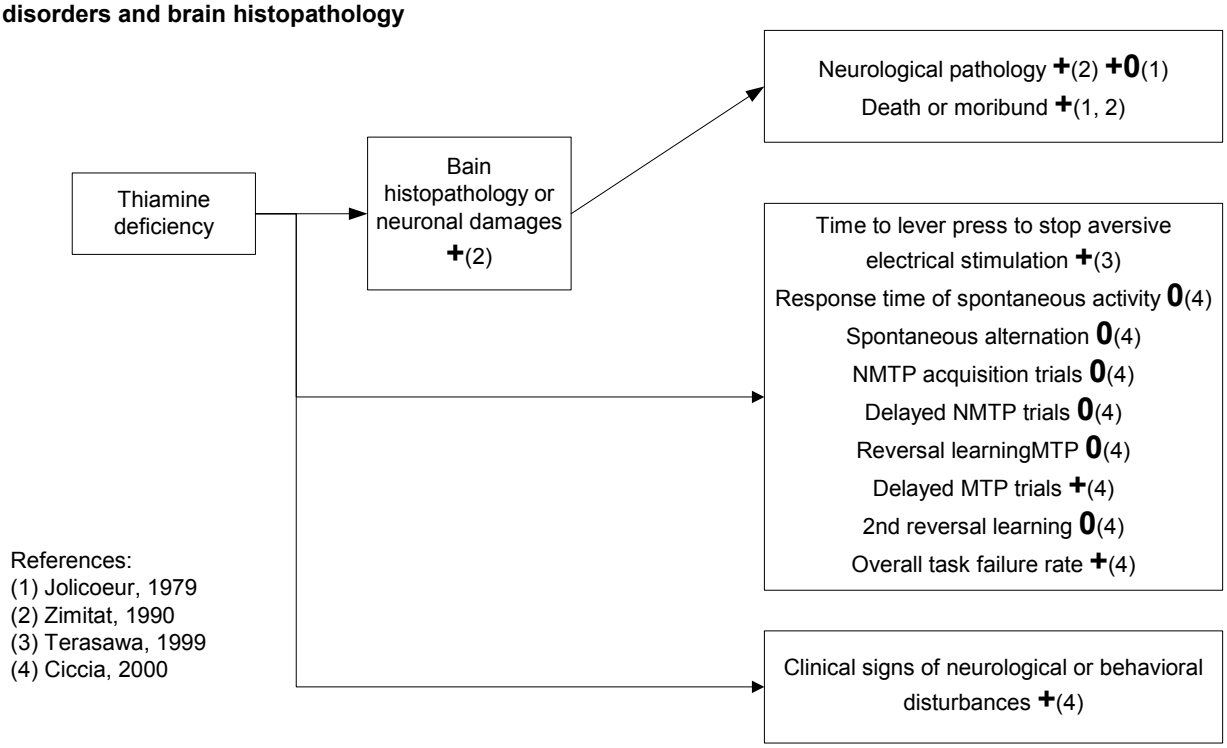
We found no study that examined the effects of riboflavin (B2) or mixed B vitamin treatments on outcomes of interest.

Overall, research has shown that there were negative effects of thiamine and folate deficiency or deprivation on animal's clinical status and/or histopathology, although not all deficient animals had worse performance in neurocognitive tests. Studies have found some positive effects of the supplementations of B6, B12, and folate on animal's performance in neurocognitive tests, but studies did not show a dose-response relationship. Only folate deficiency was examined in animal models of AD and PD; the results showed a synergistic effect with both PD and AD pathology.

Summary Findings From Studies Using Immature Animals. Eight studies in nine publications were not included in detail in this review because immature rodents were used.[43-51] In these studies, young rodents were treated for a short period time and tested before their growth ceased. Though these studies are not applicable to questions concerning "age-related neurodegenerative" changes, it is of interest how these studies compare to those with more appropriate models. Of the eight studies, three used thiamine-deficient models, two used B6-deficient models, two used a B12-supplementation model, and one used folate-deficient model. The results from these studies were similar to those summarized in this report. Detailed data can be found in the evidence tables.*

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/berry/berry.pdf.

Figure 1. Summary findings of the effects of thiamine deficiency on rats' cognitive function, movement disorders and brain histopathology



+ Normal thiamine animals performed better than thiamine-deficient animals
0 No difference between groups
– Normal thiamine animals performed worse than thiamine-deficient animals

Table 2. Thiamine deficient (intervention) vs. normal thiamine (control) diets

Study, Year	Model	Age/Weight	Duration	Intervention (B1 dose)	N	Control (B1 dose)	N	Neurocognitive Test / Clinical Pathology	Results	*P*	Histology Measure	Results	*P*	Quality
Jolicoeur, 1979 (2 papers)	Rats	Male Sprague Dawley, 275-350 g	44 days	0	6	Purina Rat Chow (nd)	6	Neurological pathology[c] followed by deaths	+	<.05				B
								Catalepsy, rigidity, and landing foot spread	0					
Zimitat, 1990	Rats	Female Wistar, 9 wk	35 wk	0	36 /11[d]	8 or 50 mg/kg of diet[e]	36/17[d]	Ataxia, opisthotonus, moribund	+	<.001	Hemorrhages, necrosis & vacuolation[g]	+	nd	B
Terasawa, 1999	Rats	Wistar, 260-300 g	~42 days	30 mg/100 g of diet	5	60 mg/100 g of diet	5	Time to lever press to stop aversive electrical stimulation	+	nd				C
Ciccia, 2000	Rats	Male Sprague Dawley, ~2 mo	8 mo	Vitamin-fortified chow + 3 episodes of TD, each of which lasted ~4.5 wk at wk 10, 18, and 26 of treatment	~12[f]	Vitamin-fortified chow + 1 mg/kg BW i.p. 3 times/wk (Monday, Wednesday, Friday)	~14[f]	Response time of spontaneous activity	0					B
								Spontaneous alternation	0					
								NMTP acquisition trials	0					
								Delayed NMTP trials	0					
								Reversal learning MTP	0					
								Delayed MTP trials	+	<.0001				
								2nd reversal learning	0					
								Overall task failure rate	+	nd				
								Clinical signs of neurological or behavioral disturbances	+	nd				

Model=Animal, Strain; BW = body weight; i.p. = intraperitoneal; NMTP = nonmatching-to-position; MTP = matching-to-position; wk = week

[c] Less locomotor activity, lost the righting reflex, displayed impaired weight shift responses
[d] Number tested for clinical symptoms / Number tested for histopathology
[e] Control group = 8 mg/kg, 2 thiamine fortified groups = 50 mg/kg. No difference among these groups
[f] At different stages of behavioral testing, 5 control rats and 2 thiamine deficient rats either died of unknown causes or developed tumors and were killed. Thus, group sizes reported on each behavioral task are different
[g] Pathologies seen primarily in the medial vestibular nucleus

+ Normal thiamine animals performed better than thiamine-deficient animals
0 No difference between groups
– Normal thiamine animals performed worse than thiamine-deficient animals

Table 3. Vitamin B6 supplementation (intervention) vs. normal B6 (control) diets in healthy animals

Study, Year	Model Age/Weight	Duration	Intervention (B6 dose)	N	Control (B6 dose)	N	Neurocognitive Test	Groups	Results	*P*	Quality
Tunnicliff, 1972	Mice	Male C57BL/6J & DBA/2J inbred strain, 9 wk	4 wk	3 μg/day B6-HCl[a]	15	None		Active escape learning: mean score & variance	All	**0**		B
				15 μg/day B6-HCl[a]	20							
				150 μg/day B6-HCl[a]	15			Passive avoidance learning: mean score & variance	All	**0**		
								Locomotor activity: mean score	All	**0**		
								Locomotor activity: variance	3 μg	**Ref**		
									15 μg	**–**	<.01	
									150 μg	**+**	<.01	
Driskell, 1973	Rats	Female, 220 g	3 wk	15 μg/15 g diet	6	None	6	Activity and curiosity	15 μg	**–**	<.01	A
				30 μg/15 g diet	6				30 μg	**–**	<.01	
				45 μg/15 g diet	6				45 μg	**0**		
				60 μg/15 g diet	6				60 μg			
				75 μg/15 g diet	6				75 μg			
				90 μg/15 g diet	6				90 μg			
								T maze	All	**0**		

B6-HCl = pyridoxine hydrochloride; i.p.= intraperitoneal

[a] The amount of B6 was estimated based on each animal drank approximately 5 mL of water and ate about 5 g of food each day

+ B6 supplemented animals performed better than normal B6 (or reference) animals, or normal B6 animals performed better than B6-deficient animals
0 No difference between groups
– B6 supplemented animals performed worse than normal B6 (or reference) animals, or normal B6 animals performed worse than B6-deficient animals

Table 4. Vitamin B12 supplements (intervention) vs. normal B12 (control) diets in diseased animals

Study, Year	Model	Age/Weight	Duration	Intervention (B12 dose)	N	Control (B12 dose)	N	Neurocognitive Test	Results	*P*	Quality
Masuda, 1998	Rats	Wistar w/ NBM lesions	10-18 days	1.0 mg/kg	10	Standard rat chow (0.001 mg/ kg B12)	10	Spontaneous movements	**0**		A
								Morris water maze – Acquisition	**0**		
								Morris water maze – Retention	**0**		

i.p. = intraperitoneal; NBM = nucleus basalis magnocellularis; Model = Animal, Strain or cell

+ B12 supplemented animals performed better than normal B12 animals
0 No difference between groups
– B12 supplemented animals performed worse than normal B12 animals

Table 5. Folate deficiency (intervention) vs. normal folate (control) diets

Study, Year	Model	Age/Weight	Duration	Intervention (folate dose)	N	Control (folate dose)	N	Neurocognitive test	Results	*P*	Biochemical / Histology measure	Results	*P*	Quality
Deficient – normal animal model														
Kim, 2002	Rats' brains	Male Sprague Dawley, 6 mo	8 wk	0	8	4 mg folate/kg diet	8				Degenerative appearance of cerebrocortical microvascular wall	+	nd	A
Duan, 2002	Mice	C57B1/6, 2 mo, 21-23 g	3 mo	0	10	2 mg folate/kg diet	10	Rotarod apparatus (time) Rotarod apparatus (number of falls)	**0** **0**		Loss of dopaminergic neurons in substantia nigra	**0**		A
Deficient – Parkinson's disease model														
Duan, 2002	Mice	C57B1/6 2 mo / 21-23 g	3 mo	0 mg folate/kg diet + 2 i.p. MPTP (20 mg/kg B.W.)	10	2 mg folate/kg diet + 2 i.p. MPTP (20 mg/kg B.W.)	10	Rotarod apparatus (time) Rotarod apparatus (number of falls)	**+** **+**	<.01 <.01	Loss of dopaminergic neurons in substantia nigra	**+**	<.01	A
Deficient – Alzheimer's disease model														
Kruman, 2002	Mice	"Swedish" APP mutant, 7 mo	3 mo	0 mg folate/kg + 4.5 gm/kg Hcy diet	nd	Standard mouse diet (folate: nd; Hcy : 0 mg/kg diet)	nd				Aβ deposition Aβ1-42/Aβ1-40 ratio Loss of neurons in regions CA3 of hippocampus Loss of neurons in regions CA1 of hippocampus	**0** **0** **+** **0**	<.0001	B

i.p. = intraperitoneal; Model=Animal, Strain; B.W.=body weight; APP=amyloid precursor protein; Hcy=homocysteine; Aβ=amyloid β-peptide; mo = months; wk = weeks

+ Normal folate animals performed better than folate deficient animals
0 No difference between groups
– Normal folate animals performed worse than folate deficient animals

Effects of B Vitamins on the Expression or Function of Alzheimer's Disease-Related Genes

Study Descriptions. Only one animal study with 3 publications[52-54] and one in vitro study[55] examined the effects of B vitamins on the expression or function of AD-related genes. Both are of high quality.

Overall Effects. Shea et al. published a series of papers to test a hypothesis that deficiencies in apolipoprotein E gene (ApoE) function are associated with increased oxidative stress in the central nervous system (CNS). ApoE can promote neuronal survival and outgrowth and may play important roles in adaptive responses to aging and brain injury.[11] The experiments were carried out by comparing the responses of transgenic mice lacking ApoE with those of normal mice of the identical genetic background to dietary oxidative stress induced by folate deprivation and by inclusion of excess iron in their diet. The mice used in this series of experiments were overlapped. (The source of this information was a personal communication with the authors.) Both transgenic mice and normal mice were fed either an experimental diet (without folate) or a control diet (with 4 mg folic acid per kilogram of diet) for 1 month; then harvested total CNS tissue was analyzed for thiobarbituric acid-reactive substances (TBARS, an end-point index of oxidative damage), and total antioxidant capacity in CNS. ApoE-deficient mice were found to have significantly increased TBARS when challenged with iron (which induces oxidation) in the absence of folate, in contrast to ApoE-deficient mice challenged with iron in the presence of folate and to normal mice, regardless of folate or iron status. Furthermore, antioxidant capacity was lower in ApoE-deficient mice receiving iron in the absence of folate compared to same mice receiving folate or compared to normal mice, regardless of folate status. These results suggest that the genetic deficiency of a complete absence of ApoE could be alleviated with 4 mg/kg body weight folic acid repletion for 1 month. This is proposed as a partial explanation as to why certain ApoE alleles are associated with increased prevalence and earlier onset of AD.

Fuso 2005 conducted an in vitro study using neuroblastoma cell lines and examined the effects of folate and vitamin B12 deficiency on AD gene and protein expression. Specifically, they examined APP, presenilin-1 (PS1) and presenilin-2 (PS2), the genes linked to familial AD.[11] For the purpose of this review, we chose the most appropriate comparisons for our questions of interest, which were the results from cells grown in the vitamin deprived media versus cells grown in the differentiation media, because the only difference in the contents of these two media are the amount of folate and B12. The results showed that folate and vitamin B12 deprivation did not change APP or PS2 gene and protein expressions, but increased PS1 gene and protein expression.

Summary. A series of animal experiments showed that ApoE-gene knockout mice are less capable of buffering oxidative challenge in CNS than the normal mice, and the genetic deficiency of a complete absence of ApoE could be alleviated with folate repletion. The results from the other in vitro study demonstrated that an increase in PS1 gene could be induced by folate and vitamin B12 deprivation. The other genes involved in APP processing, and APP itself seemed to be independent of folate and vitamin B12 deprivation.

Effects of B Vitamins on Blood Brain Barrier or Cerebrovascular Endothelial Function

Study Descriptions. Five studies on the effects of B vitamins on BBB or cerebrovascular enthothelial function are included in this section (Table 6).[56-60] Of these, two moderate quality studies and one high quality study examined BBB transport and permeability in normal and thiamine-deficient rats. Two high quality studies examined the effects of dietary folate supplementation on cerebral endothelial function and cerebral vascular damage induced by hyperhomocysteinemia in vivo.

Overall Effects

Thiamine (B1) deficiency. Warnock 1968 examined pyruvate metabolism and the differences in pyruvate transport across BBB, comparing normal rats to thiamine-deficient rats.[58] The results showed that labeled pyruvate entered the brain directly in adult thiamine-deficient animals, while it did not directly enter the brain of normal adult animals. This indicated that selective transport across BBB was not functioning in a normal fashion in thiamine-deficient rats. Robertson 1971 evaluated the presence or absence of extravascular fluorescence bound to intraperitoneally administered bovine albumin in relation to the severity of BBB lesions.[60] They found that extravascular fluorescence was present in one of 24 rat brains from animals with early stage of thiamine deficiency (as indicated histologically by slight edema, or more marked spongy reticulation, frequently accompanied by vascular congestion). Extravascular fluorescence was present in 12 of 22 rat brains from animals with late stage of thiamine deficiency (as indicated histologically by hemorrhages, tissue degradation and neuronal fallout). There was no extravascular fluorescence seen in rat brains from control animals. These results suggested that BBB is intact with respect to albumin in the early lesions of thiamine deficiency. Thus intracellular edema associated with early deficiency results from a defect in cell membrane transport rather than a vascular leak of the inflammatory type across BBB. A follow-up study by Manz 1972 employed a similar protocol to further define the nature and sequence of permeability changes of the BBB, using horseradish peroxidase (a low molecular weight protein marker).[59] It was found that control rats and rats with early stages of thiamine deficiency had "qualitatively and quantitatively" the same pattern of peroxidase granules in phagocytes. None of the rats with early stage of thiamine deficiency had parenchymatous infiltration, while 21 of 30 rats with late stage thiamine deficiency did. Furthermore, control rats and rats with early stage of thiamine deficiency were devoid of peroxidase in the vascular basement membrane and the neural parenchyma. Although the interendothelial junctional complexes were morphologically intact in rats with late stage of thiamine deficiency, reaction product was deposited in the contraluminal side basement membrane zone of intercellular gaps. These results suggested that BBB damage seen in later stages corresponds to damage seen from cold-injury edema and other models of cerebral edema. The leakage of BBB appears to be predominantly through the mechanism of pinocytosis (introduction of fluids into a cell by invagination of the cell membrane, followed by formation of vesicles within the cells), not disruption of interendothelial junctions.

Folate supplementation. Lee et al. conducted a series of studies to examine the effects of dietary folate supplementation on cerebral endothelial function and cerebral vascular damage induced by hyperhomocysteinemia in vivo. Before allocation to dietary intervention, all rats were fed a diet with added homocysteine (3.0 g per kg diet) for 2 weeks to induce hyperhomocysteinemia along

with the hyperhomocysteinemia-induced cerebrovascular endothelial dysfunction. The first study found that 2 weeks of dietary folate supplementation significantly ameliorated the hyperhomocysteinemia-induced cerebrovascular endothelial dysfunction, characterized by reduced endothelial nitric oxide synthase (eNOS) activity and glucose transporter protein (GLUT-1) activity. Specifically, the level of brain eNOS protein expression increased by 44 percent (P=0.04) and the GLUT-1 level increased by 27 percent (P=0.04), in the comparison of rats fed an additional 8 mg per kg diet of folate to those on homocysteine diet. However, an unexpected result was observed for the cerebral content of the vascular cell adhesion molecule (VCAM-1). Rats fed an additional 8 mg per kg diet of folate had a 43 percent (P=0.04) decrease in VCAM-1 level. A subsequent study evaluated the effects of 8 weeks of dietary folate supplementation on cerebral vascular damage induced by hyperhomocysteinemia in vivo, in particular, investigating the structural features of the cerebral vasculature by electron microscopy. Consistent with the results from the first study, folate supplementation significantly increased the cerebral GLUT-1 protein, which had been decreased by a homocysteine diet. In the folate supplemented group, damaged vessels, annihilation of cell organelles, degeneration of mitochondrial bilayer, and perivascular detachment were also observed, although the damage of the cerebral vasculature was described as “more serious” in rats fed homocysteine-supplemented diet. In addition, dietary supplementation with folate for 8 weeks significantly reduced the percentage of damaged vessels.

Summary. Three studies examined BBB transport and permeability showed an abnormal selective transport of pyruvate across BBB in adult thiamine-deficient animals and intracellular edema associated with early deficiency results from a defect in cell membrane transport rather than a vascular leak of the inflammatory type across BBB. The leakage of BBB appears to be predominantly through the mechanism of pinocytosis, not disruption of interendothelial junctions. Two studies examined the effects of dietary folate supplementation on cerebral endothelial function and cerebral vascular damage induced by hyperhomocysteinemia in vivo. The results suggest that folate supplementation may ameliorate the hyperhomocysteinemia-induced cerebrovascular endothelial dysfunction and reduce cerebrovascular damage induced by hyperhomocysteinemia.

Table 6. Effects of B vitamins on blood brain barrier or cerebrovascular endothelial function

Study, Year	Model		Duration	Intervention (vitamin B dose)	N	Control (Vitamin B dose)	N	BBB or cerebrovascular endothelial function outcomes		Results	*P*	Quality
Thiamine deficiency in normal animals												
Warnock, 1968	Rats	Male S-D, 50-65 g	nd[a]	"Thiamine deficient diet"	15	"Thiamine adequate diet"	10	Pyruvate-2-14C entered the brain directly in adult thiamine deficient animals		+	nd	B
Robertson, 1971	Rats	Female Long Evans or Wistar Furth strains, Immature	28-46 days	Synthetic thiamine-free diet (0)	46	Intervention diet w/ thiamine HCl 40 µg/100 g B.W. i.p.	10	Integrity of BBB with respect to absence of extra-vascular plasma proteins	Early stage of TD: slight edema; marked spongy reticulation	Ref[c]	<.001	B
									Late stage of TD: hemorrhages, tissue degradation and neuronal fallout	+		
Manz, 1972	Rats	Female Wistar Furth strains, Immature	30-45 days	Synthetic thiamine-free diet (0)	37	Intervention diet w/ thiamine HCl 40 µg/100 g B.W. i.p.	12	Diffuse parenchyma-tous infiltration of the vestibular area	Controls and early stage of TD (edema only)	Ref	<.001	A
									Late stage of TD: hemorrhage and necrosis	+		
								Peroxidase was deposited in the contraluminal side basement membrane zone of intercellular gaps, but interendothelial junctional complexes were morphologically intact, in rat brains with late stage of TD			nd	
Folate Supplementation in deceased animals												
Lee, 2004	Rats[b]	Male S-D, 8 wk	2 wk	8 mg/kg diet + 0.3% Hcy	6	0.3% Hcy	6	Cerebral expression level of GLUT-1		+	.04	A
								Cerebral expression level of VCAM-1		–	.04	
								Endothelial nitric oxide synthase		+	.04	
Lee, 2005	Rats[b]	Male S-D, 8 wk	8 wk	8 mg/kg diet + 0.3% Hcy	4	0.3% Hcy	4	Cerebral expression level of GLUT-1		+	<.05	A
								Damaged cerebral capillary wall structure		+	nd	
								% Damaged vessels in the hippocampus		+	<.05	

BBB = blood brain barrier; S-D=Sprague-Dawley; Hcy=homocysteine; GLUT-1=glucose transporter protein; VCAM-1= vascular cell adhesion molecule; i.p.= intraperitoneal; B.W.=body weight; TD=thiamine deficiency

[a] At first signs of polyneuritis
[b] Rats were fed a diet with 0.3% Hcy for 2 weeks before allocated to the intervention or control diets described in the table. All rats had induced hyperhomocysteinemia before the allocation.
[c] Extravascular fluorescence was not seen in control animals (n=10)

+ B vitamin deficient animals have abnormal function while normal B vitamin animals have normal function, or B vitamin supplemented animals have better function than normal B vitamin animals
0 No difference between groups
– B vitamin supplemented animals have worse function than normal B vitamin animals

Human Studies

The human studies addressing the evidence of the effect of B vitamins on age-related neurodegenerative conditions fall into three types, which will be discussed in the following order: intervention trials, studies of associations between B vitamin intake and neurocognitive function, and studies of association B vitamin tissue levels and neurocognitive function.

Among the 85 human studies reviewed, 30 were intervention trials, eight were B vitamin intake association studies, and 52 were B vitamin level association studies. Five studies reported data on both interventions and associations (at baseline). The large majority of studies were deemed to be of poor quality. Overall, three studies were of good quality, 25 of fair quality, and 57 of poor quality. The most common reasons for grading study quality poor were lack of randomization or control in intervention studies, lack of adjustment for potential confounders in association studies, and poor or inadequate reporting of study design and results. Overall, 23 studies had broad applicability, 40 had moderate applicability, and 23 had narrow applicability, often due to small sample size or focus on a specific population of diseased individuals. (One article contained two studies with different applicability ratings.)

Tables 7 and 8 provide an overall summary of the number of studies, number of subjects, quality, applicability, and summarized results of the evidence for B vitamin intervention (Table 7) and B vitamin intake and levels associations (Table 8) with neurocognitive conditions.

Table 7. Summary of intervention studies evaluating the effect of B vitamins on neurocognitive outcomes.

	INTERVENTION STUDIES									
	Change Severity					Prevent/Delay Disease				
Vitamin	Studies	N	Quality	Applicability	Results	Studies	N	Quality	Applicability	Results
B1	5	79	A 0 B 0 C 5	III 0 II 2 I 3	↔	1	32	A 0 B 0 C 1	III 0 II 1 I 0	↑
B2	0					0				
B6	2	151	A 0 B 1 C 1	III 0 II 1 I 1	↔	0				
B12	12	492	A 1 B 2 C 10	III 0 II 5 I 8	↔	1	14	A 0 B 0 C 1	III 0 II 0 I 1	↔
Folate	5	168	A 0 B 2 C 3	III 0 II 3 I 2	↔	0				
Mix	6	462	A 0 B 2 C 4	III 1 II 4 I 1	↔	0				

Quality: A = good quality; B = fair quality; C = poor quality.
Applicability: III = widely applicable; II = moderately applicable; I = narrowly applicable.
Results: ↑ = treatment with, higher intake of, or higher level of associated with beneficial outcome (lessened severity, lower incidence)
↔ = no association
↓ = associated with worsened outcome (increased severity, higher incidence).

Table 8. Summary of association studies evaluating the association of B vitamin intake or levels on neurocognitive outcomes.

	INTAKE STUDIES										LEVELS STUDIES									
	Associated w/Severity					Associated w/Prevalence or Incidence					Associated w/Diagnosis					Associated w/Severity				
Vitamin	Studies	N	Quality	Applicability	Results	Studies	N	Quality	Applicability	Results	Studies	N	Quality	Applicability	Results	Studies	N	Quality	Applicability	Results
B1	3	727	A 0 B 2 C 1	III 0 II 3 I 0	↔	1	62	A 0 B 0 C 1	III 0 II 1 I 0	↔	7	394	A 0 B 1 C 3	III 2 II 2 I 3	↔	1	201	A 0 B 1 C 0	III 1 II 0 I 0	↔
B2	3	727	A 0 B 2 C 1	III 0 II 3 I 0	↔	1	62	A 0 B 0 C 1	III 0 II 1 I 0	↔	2	154	A 0 B 0 C 2	III 0 II 2 I 0	↔		0			
B6	4	539	A 0 B 3 C 1	III 0 II 3 I 1	↔	2	136,185	A 1 B 0 C 1	III 2 II 0 I 0	↔	8	1,587	A 0 B 2 C 6	III 2 II 3 I 3	↔	2	141	A 0 B 2 C 0	III 0 II 2 I 0	↔
B12	3	530	A 0 B 3 C 1	III 0 II 2 I 1	↔	2	136,120	A 1 B 0 C 1	III 1 II 1 I 0	↔	26	8,093	A 1 B 9 C 16	III 12 II 10 I 4	↔	7	2,618	A 0 B 5 C 2	III 2 II 4 I 1	↔
Folate	3	530	A 0 B 3 C 1	III 0 II 2 I 1	↔	3	136,248	A 1 B 0 C 2	III 2 II 1 I 0	↔	28	8445	A 1 B 11 C 16	III 10 II 17 I 1	↑	6	1,663	A 0 B 4 C 2	III 3 II 2 I 1	↔

Quality: A = good quality; B = fair quality; C = poor quality.

Applicability: III = widely applicable; II = moderately applicable; I = narrowly applicable.

Results: ↑ = treatment with, higher intake of, or higher level of associated with beneficial outcome (lessened severity, lower incidence)

↔ = no association

↓ = associated with worsened outcome (increased severity, higher incidence).

Effect of B Vitamin Supplementation on Neurocognitive Function

Thiamine (Vitamin B1) Intervention Studies

Study Descriptions. Three randomized controlled trials (RCTs),[61-63] one non-randomized comparative trial (N-RCT),[62] and one uncontrolled cohort study[64] reported data on thiamine supplementation among patients with probable or possible AD in four articles. All studies included subjects whose mean ages were greater than 70 years, and who met standard criteria for diagnosis of probable or possible dementia. Their average mini-mental status examination (MMSE) scores ranged from 14 to 18, indicating moderate to mild dementia. All RCTs tested three divided doses of 3 g per day thiamine, the N-RCT tested a maximum of 8 g per day thiamine and the single arm intervention trial tested a dose of 750 mg of a thiamine derivative. Thus, most studies used high-dose interventions compared to the US Recommended Daily Allowance (RDA) of 1.1 to 1.2 mg daily. The primary outcome for all studies was cognitive function (measured with MMSE or Alzheimer's Disease Assessment Scale [ADAS]). In addition, two of the studies evaluated outcomes on behavior and/or emotion.[61,64] All studies had small sample sizes (fewer than 25 subjects). All studies were assessed to poor quality (C). Two studies have moderate applicability and three narrow applicability.

Overall Effect. Three of the five studies reported statistically significant effects in cognitive function after intervention with thiamine for short durations (1 to 3 months).[61,62,64] Meador 1993 reported statistically significant improvement of cognitive score (ADAS) in the initial months with reduced deterioration at 11 to 13 months, suggesting some beneficial effect of high dose of thiamine in decreasing the rate of progression of AD. This study also reported clinically significant effect of thiamine supplementation in the majority of subjects at dosages above 4 g per day.

Among these, Blass 1988 was a randomized crossover trial. The study did not document a wash out phase and compared thiamine to the intervention of niacinamide 750 mg as an active placebo. The follow-up study to Blass 1988, by Nolan 1991, was an RCT with parallel design that compared thiamine treatment to lactose placebo. It found no significant effects on cognitive function after treating to the same dose of thiamine for one year.

Meador 1993 reported two different experiments, and tested higher doses of thiamine (greater than 3 g per day). The first was a crossover RCT that compared thiamine to placebo without a washout phase between treatments. The second was a non-randomized comparative trial, which gave AD subjects sequentially higher doses of thiamine followed by placebo, and reported statistically significant improvements in the cognitive score (ADAS) at 3 dosages of 4 g per day or more thiamine. Of note this thiamine supplementation study reported improvement in the scores of Clinical Global Impression of Change (CGIC), which is a physician rated assessment of overall change from the baseline. However the study reported results among fewer than 10 subjects for dosages of 7 g or more between 8 to 13 months.

Mimori 1996 was an uncontrolled cohort study that used fursultiamine, a thiamine derivative that is easily converted into an active form of thiamine in the body. They evaluated nine people with AD and normal mean levels of blood thiamine. The study reported a statistically significant improvement in cognitive function (MMSE) and the emotional component of the Gottfries-Brane-Steen (GBS) score after the intervention with fursultiamine. Blood thiamine levels increased markedly after fursultiamine intervention.

Interactions and Covariates. In its second experiment, Meador 1993 tested a maximum dose of thiamine for 13 months. The first phase of the study the thiamine dose was incrementally increased each month to a maximum of 6 g per day. In the second phase a "best dose" (defined as achievement of best ADAS scores) was used, and in the third phase a maximum dose of 8 g per day was achieved. However, after month 5, the results for the doses greater than 6 g of thiamine were reported only in a small subset of two to six subjects. High dose thiamine significantly reduced ADAS scores compared to baseline, but MMSE showed no significant change. No other interactions were reported in the studies. Only the uncontrolled cohort study reported blood levels of thiamine before intervention, and included subjects with normal blood levels. All the studies of thiamine intervention used tests of the same domain and measured global cognitive function as the outcome.

Summary. Five poor quality studies assessed in four articles reported data on the effect of thiamine intervention among people with probable or possible AD. Overall, two RCTs, and one cohort study reported improvement in cognitive function during short-term treatment of thiamine. However, without a comparable control group, it is difficult to assess the validity of the uncontrolled cohort study given the variable course of dementia over time. Two long-term studies failed to show any discernable differences in cognitive function as measured by MMSE. However the N-RCT that supplemented AD subjects with progressively higher doses of thiamine followed by placebo reported statistically significant improvement of cognitive score (ADAS) in the initial months with reduced deterioration at 11 to 13 months, suggesting some beneficial effect of high dose of thiamine intervention. This study also reported long-term clinical benefit from thiamine intervention.

Table 9. Effect of thiamine (vitamin B1) intervention on cognitive function tests

Design								Change		Net Change				
Author Year	Duration	Intervention Dose g/day Control	Route	N	Test /Subtest	Maximum Score	Base value	Value	*P value* Change	Value	*P value* Net Change	Population	Mean Age (yr)	Applicability Quality
RCT [a]														
Blass 1988	3 mo	3 Niacinamide 750 mg	po	11 11	MMSE ↑	30	14.2 14.2	+1.3 +0.5	*.08* *NS*	+0.7	<.001	AD	72 ♂	C
Meador 1993 Study 1	1 mo	3 Placebo	po	17 17	MMSE ↑	30	18 18	0 -1	*NS* nd	+1	nd	AD	71 ♂♀	C
		3 Placebo	po	17 17	MMSE ↑	30		69%↓ [b] 79%↓ [b]	*NS* *<.03*	-10%↓ [b]	NS			
Nolan 1991	12 mo	3 Placebo	po	55 55	MMSE ↑	30	16.6 16.0	-6.2 -1.4	<.05 <.05	-4.8	nd	AD	76 ♂	C
Meador 1993 Study 1	1 mo	3 Placebo	po	17 17	ADAS ↓	120	36 36	+2.1 +6.7	nd	-3	nd	AD	71 ♂♀	C
		3 Placebo	po	17 17	ADAS ↓	120		56%↓ [c] 75%↓ [c]	*NS* *<.04*	-19%↓ [c]	<.02			
Blass 1988	3 mo	3 Niacinamide 750 mg	po	11 11	Blessed ↑	nd	7.4 7.4	+0.1 -0.5	*NS* *NS*	+0.6	NS	AD	72 ♂	C
		3 Niacinamide 750 mg	po	11 11	Haycox ↑	nd	11.1 11.1	+2.3 +1.2	*NS* *NS*	+1.2	NS			
N-RCT														
Meador 1993 Study 2	1 mo [d]	4 Placebo	po	17 15	MMSE ↑	30	21.2 21.5	+0.5 +0.4	NS NS	+0.1	nd	AD	71 ♂♀	C
		5 Placebo	po	17 15	MMSE ↑	30	21.2 21.5	+0.6 +0.4	NS NS	+0.2	nd			
		6 Placebo	po	17 15	MMSE ↑	30	21.2 21.5	+0.5 +0.4	NS NS	+0.1	nd			
Meador 1993 Study 2	1 mo [d]	4 Placebo	po	16 13	ADAS ↓	120	27.2 26.2	-3.8 -2.1	≤.01 NS	-1.7	nd	AD	71 ♂♀	C
		5 Placebo	po	16 13	ADAS ↓	120	27.2 26.2	-3.8 -2.1	≤.05 NS	-1.7	nd			
		6 Placebo	po	16 13	ADAS ↓	120	26.6 26.2	-2.3 -2.1	NS NS	-0.2	nd			
Cohort														
Mimori 1996	3 mo	Fursultiamine 100 mg [e]	po	9	MMSE ↑	30.0	17.2	+2.2	<.05			AD	72 ♂	C
					Hasegawa Dementia Scale ↑	32.5	17.0	+0.6	NS					
					GBS ↑	228	59.8	-7.4	<.10					

↑ Higher score indicates better cognitive function. ↓ Lower score indicates better cognitive function. MMSE, mini-mental status examination; ADAS, Alzheimer disease assessment scale; Blessed, behavioral rating according to Blessed et al.; GBS, Gottfries-Brane-Steen scale; Haycox, behavioral scale of Haycox; mo, month; po, orally.

[a] Blass 1988, and Meador 1993 are crossover trials.
[b] Proportion (or calculated net proportion) of patients with lower MMSE score (deterioration).
[c] Proportion of patients with ADAS higher score (deterioration).
[d] The different doses of thiamine were supplemented sequentially, for one month each, followed by placebo.
[e] Fursultiamine (thiamine tetrahydrofurfuryl disulfide hydrochloride) a derivative of thiamine.

Riboflavin (Vitamin B2) Intervention Studies

No prospective trial has evaluated the effect of vitamin B2 treatment on neurocognitive function.

Vitamin B6 Intervention Studies

Study Descriptions. Two RCTs assessed the effect of B6 intervention on cognitive function in humans.[65,66] They included 75 and 38 cognitively intact subjects in the intervention arm respectively. One RCT used 75 mg of B6 per day for 5 weeks while the other trial administered 20 mg of B6 per day for 12 weeks. Both doses are considerably higher than the US RDA dose of 1.3 to 1.7 mg daily. One study used digit symbol coding, vocabulary test, and digit span-backwards from WAIS III as well as the Stroop test for executive function and initial letter for verbal fluency. The second RCT applied the Associate Recognition Task and the Long Term Memory Storage to assess cognitive function. The trials were of moderate (B) and low (C) quality and had narrow and moderate applicability, respectively.

Overall Effect. Deijen 1992 reported a significant decrease in Long Term Memory Storage for the intervention group, which corresponds to memory improvement ($P<0.03$). However, no significant effect was recorded in the Associate Recognition Task for the intervention group in the same study. However, no formal comparison between intervention and placebo group was provided in the article and no information is given for the significance of the changes in the placebo group.

Interactions and Covariates. There is no adequate evidence to support any dose effect of B6 on the outcomes. There was no evidence across studies of differences in effect on tests of different cognitive domains. No other interactions were reported in the studies.

Summary. Two RCTs of moderate and low quality, with narrow and moderate applicability for cognitively intact populations investigated the effect of B6 intervention on cognitive function in humans. With treatment, a significant improvement was found with one cognitive function test. It is uncertain whether this change is of any clinical benefit. It is also unclear whether the changes with treatment were significantly different than changes in the control arm in the same study. No other significant effect was reported in the studies. Because of the very limited evidence no conclusions can be drawn for the effect of B6 on preventing cognitive function decline.

Table 10. Effect of vitamin B6 intervention on cognitive function tests

Design		Intervention							Change		Net Change					
Author Year	Duration	Dose mg/day	Route	N	Test /Subtest	Maximum Score	Base value	Value	*P value* Change	Value	*P value* Net Change	Population	Mean Age (yr)	Applicability	Quality
RCT															
Bryan, 2002	5 wk	75	po	75	Digit-Symbol Coding ↑ (WAIS III)	nd	63.4	+7.3	NS	+2.5	NS	Normal	74	🧍	B
		Placebo					62.3	+4.8	NS						
		75	po	75	Verbal Ability: Vocabulary ↑ (WAIS III)	nd	22.1	+0.6	NS	+0.8	NS				
		Placebo					21.9	-0.2	NS						
		75	po	75	Digit Span-Backwards ↑ (WAIS III)	nd	6.1	0	NS	-0.4	NS				
		Placebo					7.1	+0.4	NS						
		75	po	75	Stroop ↑	nd	2.34	-0.06	NS	+0.06	NS				
		Placebo					2.51	-0.12	NS						
		75	po	75	Verbal Fluency: Initial letter ↑	nd	29.3	+1.2	NS	-2.1	NS				
		Placebo					23.7	+3.3	NS						
Deijen, 1992	12 wk	20	po	38	Associate Recognition Task[a] ↑	9	3.2[b]	+0.1	NS	*+1.2*	nd	Normal	83	🧍🧍	C
		Placebo		38			3.9[b]	-1.1	nd						
		20		38	Long Term Memory Storage[c] ↓	9	0.35	-0.35	<.03	*-0.8*	nd				
		Placebo		38			0.45	+0.45	nd						

↑ Higher score indicates better cognitive function. ↓ Lower score indicates better cognitive function. WAIS, Wechsler Stroop, Stroop Color-word Test; po, orally

[a] Test of long term verbal memory, same as Associate Learning Task with 1 hour delay.
[b] Results reported graphically.
[c] Difference (by subtraction) between Associate Learning and Recognition Tasks (what is forgotten), also known as Forget Score.

Cobalamin (Vitamin B12) Intervention Studies

Study Descriptions. Five RCTs, one N-RCT, and seven uncontrolled cohort studies assessed the effect of B12 intervention on cognitive function in humans.[65,67-78] Among the RCTs (Table 11) sample size ranged from 18 to 70 in the intervention arms. Two RCTs recruited cognitively intact participants with normal B12 while another two recruited cognitively intact subjects with low B12 levels. Low B12 levels was defined as 136 to 203 pg/mL in one RCT and less than 163 pg/mL in the other. The fifth RCT included subjects with cognitive impairment. The five RCTs used different doses and routes of B12 interventions ranging from 0.01 mg B12 per day orally to 1 mg 3 times per week B12, intramuscularly. Two trials used oral B12, the remainder intramuscular. B12 doses were higher than the US RDA of 2.4 μg per day. Almost all trials implemented more than one cognitive function test. MMSE was used by three trials, several parts of the Wechsler Adult Intelligence Scale (WAIS) by two trials while a number of miscellaneous tests were also reported (Table 12)., including the Cognitive Subscale of Cambridge Examination for Mental Disorders of the Elderly (CAMCOG), 12 word learning test – immediate and delayed – Stroop, initial letter from verbal fluency, memory quotient, lower and upper limit of retention span, visual and verbal memory, verbal and performance Intelligence Quotient (IQ). RCTs were of moderate to low quality (1A, 2B, 2C) and had narrow to moderate applicability.

Among the N-RCT and the cohort studies (Table 12), sample size ranged between 14 and 56. Three studies recruited demented participants, regardless of specific diagnosis. Two selected

only participants with low serum B12 levels defined as less than 200 pg/mL in one trial and less that 300 pg/mL in the other trial. There were three additional trials that included subjects with low B12 levels (less than approximately 200 pg/mL); one recruited cognitively impaired individuals with B12 less than 203 pg/mL and the other included cognitively intact persons with B12 values equal or less than 203 pg/mL while the third one evaluated patients with AD or other dementias and B12 values less than 190 pg/mL. Two other studies included subjects with AD, regardless of B12 status. As with the RCTs, cobalamin doses were considerably higher than the RDA. Almost all trials implemented more than one cognitive function test (Table 12). MMSE was used by five trials, Mattis' Dementia Rating Scale (DRS) by two studies, WAIS by one trial, GBS by two trials while a number of miscellaneous tests were also reported, including CAMCOG, Interview for Deterioration in Daily living activities in Dementia (IDDD) -Initiative, IDDD-Performance, Revised Memory and Behavioral Problems (RMBPC) -Memory, RMBPC-Disruptive behavior, delayed verbal word learning test, verbal fluency, similarities, trail making test, Rivermead behavioral face recognition test, Hasegawa's Dementia Rating Scale (HDS), and Consortium to Establish a Registry for Alzheimer's Disease (CERAD). The N-RCT was of low quality and had moderate applicability. Cohort studies were (by definition) of low quality (C) and had narrow to moderate applicability.

Overall Effect. Only one RCT (Hvas 2004) found a significant difference in effect on 12 word learning test at 15 minutes between the B12 and the control groups among cognitively impaired subjects. With other tests, some significant changes were found either with or without B12 supplementation, but these changes were not significantly different than each other. Kwok 1998, which included cognitively intact participants with low B12 (<163 pg/mL) revealed a significant improvement for B12 group in performance IQ; however, this was not significantly higher than the change in the control group. No other significant effects were reported in the RCTs.

Among the seven uncontrolled cohort studies, Teunisse 1996 reported that MMSE score was significantly worse after treatment among demented individuals with low B12 levels (<200 pg/mL). Ikeda 1992 found a significant improvement in Mattis' DMR scale at 2 months among people with AD, which however, was not maintained 4 months after the end of treatment. In the same study, GBS and HDS were also significantly improved at the end of treatment, but their improvement was also not maintained 4 months later. Van Asselt 2001, in the N-RCT, found that after treatment, performance on the delayed recall of verbal word learning test, similarities and verbal fluency test was significantly improved among cognitively intact subjects with low B12 (<203 pg/mL). In contrast, Teunisse 1996 noted significant deterioration in several tests including IDDD-Initiative, IDDD-Performance, and RMBPC-Disruptive behavior. The other five cohort trials found no change in cognitive function after B12 treatment.

Interactions and Covariates. RCTs reached statistical significance less often than cohort studies. When they reported significant changes, RCTs usually implied an improvement of cognitive function. Significant changes for cohort studies were not consistent, some finding improvement, some decline of cognitive function scores. There is large heterogeneity among RCTs and cohort studies in terms of dose, route, and duration of treatment and it would be difficult to support any conclusion about a potential dose effect. However, the only significant changes in cognitive score were found when B12 was injected rather than given orally. Seal 2002 directly evaluated the effect of B12 oral supplementation in two intervention arms, one receiving double the dose of the other, and compared these groups with placebo. No significant change was found when

MMSE score differences of the three groups were compared. In the cohort study by Mitsuyama 1988 five of the 14 demented participants were orally supplemented with 2 mg B12 daily while nine subjects had an additional B12 injection of 0.5 mg. Only those receiving B12 injections showed an improvement from baseline in GBS (*P* value not reported).

Ito 2001 analyzed the results based on the severity of dementia of Alzheimer's type. Both subjects with questionable or mild AD and participants with moderate or severe AD had non-significant improvement in MMSE after treatment. Abyad 2002 analyzed the results according to treatment duration for dementia before the trial. Both subjects with short-term treatment and subjects with long-term treatment improved MMSE; short-term treatment participants had a significant increase. Martin 1992 evaluated separately patients with cognitive impairment of long duration and patients with cognitive impairment of short duration. Only the subjects with disease of short duration showed a significant improvement in Mattis' DRS.

There was no evidence across studies of differences in effect on tests of different cognitive domains.

Summary. Five RCTs of narrow to moderate quality, one non-randomized comparative study, and seven cohort studies assessed the effect of vitamin B12 intervention on cognitive function in humans. All studies had narrow to moderate applicability. They evaluated populations that included normal participants, subjects with cognitive impairment, dementia, or AD. Several studies recruited only individuals with low B12 levels, however the definition for low B12 levels varied. There was large heterogeneity among studies in terms of dose and route of intervention as well as the cognitive function assessment instrument. Although several of the studies showed small changes in cognitive function, few reached statistical significance. Across studies that assessed similar populations after implementing the same test, results were conflicting. Several cohort studies revealed significant improvement while a smaller number of cohorts reported a significant decline in scores for cognitive function. However, the interpretation of these studies is difficult because they analyzed subjects who may have had variable courses of dementia over time, without using a control group for comparison. Vitamin B12 was given intramuscularly in the only RCT that found a significant effect in the treatment group compared to controls. Similarly, only cohort studies that used intravenous or intramuscular vitamin B12 reported a significant effect on cognitive function scores. However, given the lack of data directly comparing oral and injected routes of vitamin B12 and the paucity of controlled trials limits any conclusions regarding the utility of different routes of administration. There was very limited evidence whether other covariates may interact with B12 supplementation. Most studies did not take into consideration potential factors such as disease duration that may interfere with B12 effect.

Table 11. Effect of vitamin B12 intervention on cognitive function tests in randomized controlled trials.

Author Year	Duration	Intervention Dose mg/day / Control	Route	N	Test /Subtest	Maximum Score	Base value	Change: Value	Change: *P value* Change	Net Change: Value	Net Change: *P value* Net Change	Population	Mean Age (yr)	Applicability	Quality
Hvas, 2004	4 wk [a]	1/wk [b]	IM	70	MMSE ↑	30	26	+0.3	NS	+0.1	NS	Cognitive impairment	75		A
		Placebo		70			27	+0.2	NS				74		
Seal, 2002	~4 wk	0.01	po	10	MMSE ↑	30	15.4	0		-1.6	nd	Normal with low serum B12 [d]	82		B
		0.05		10			19.7	+1.0	NS [c]	-0.6			85		
		Placebo		11			19.6	+1.6					78		
Kwok, 1998	3-6 mo	1/mo [e]	IM	27	MMSE ↑	30	22.2	+0.1	NS	-0.1	NS	Normal with low serum B12 [f]	77		C
		Control		23			23.8	+0.2	NS						
Bryan, 2002	5 wk	0.015	po	75	Digit-Symbol Coding ↑ (WAIS III)	nd	62.5	+6.9	NS	+2.1	NS	Normal	74		B
		Placebo					62.3	+4.8	NS						
		0.015	po	75	Vocabulary ↑ (WAIS III)	nd	23.3	-0.3	NS	+0.2	NS				
		Placebo					21.9	-0.5	NS						
		0.015	po	75	Digit Span-Backwards ↑ (WAIS)	nd	6.7	+0.2	NS	-0.2	NS				
		Placebo					7.1	+0.4	NS						
Kwok, 1998	3-6 mo	1/mo [e]	IM	27	Digit Span ↑ (WAIS)	nd	10.4	+0.3	NS	+1.3	NS	Normal with low serum B12 [f]	77		C
		Control		23			11.6	-1.0	NS						
Hvas, 2004	4 wk [a]	1/wk [b]	IM	70	CAMCOG ↑	100	89	+1.3	.04	-0.6	NS	Cognitive impairment	75		A
		Placebo		70			89	+1.9	.001				74		
		1/wk [b]	IM	70	12 word learning test, immediate ↑	12	5	+0.2	NS	-0.2	NS		75		
		Placebo		70			5	+0.4	.04				74		
		1/wk [b]	IM	70	12 word learning test, 15 min ↑	12	2	+0.2	NS	-0.5	0.04		75		
		Placebo		70			2	+0.7	.001				74		
Bryan, 2002	5 wk	0.015	po	75	Stroop ↑	nd	2.50	-0.03	NS	+0.09	NS	Normal	74		B
		Placebo					2.51	-0.12	NS						
		0.015	po	75	Verbal Fluency: Initial letter ↑	nd	29.3	-0.1	NS	-3.4	NS				
		Placebo					23.7	+3.3	NS						
Kral, 1970	3-6 mo	0.1x5 /wk [g]	IM	18	Memory Quotient ↑	100	90	-3	NS	-7	NS	Normal	nd		C
		Control		22			88	+4	ND						
		0.1x5 /wk [g]	IM	18	Lower limit of retention ↑	nd	38	-12	NS	-8	NS				
		Control		22			45	-4	NS						
		0.1x5 /wk [g]	IM	18	Upper limit of retention ↑	nd	48	-6	NS	-1	NS				
		Control		22			45	-5	NS						
Kwok, 1998	3-6 mo	1/mo [e]	IM	27	Visual Memory ↑	nd	12.7	-3.0	NS	+0.7	NS	Normal with low serum B12 [f]	77		C
		Control		23			15.3	-3.7	NS						
		1/mo [e]	IM	27	Verbal Memory ↑	nd	7.8	-1.1	NS	+1.0	NS				
		Control		23			11.4	-2.1	NS						
		1/mo [e]	IM	27	Verbal IQ ↑	nd	58.2	+1.1	NS	+2.3	NS				
		Control		23			60.1	-1.2	NS						
		1/mo [e]	IM	27	Performance IQ ↑	nd	74.9	+5.8	<.005	+7.3	NS				
		Control		23			84.3	-1.5	NS						

↑ Higher score indicates better cognitive function. ↓ Lower score indicates better cognitive function. MMSE, mini-mental status examination; WAIS, Wechsler Adult Intelligence Scale CAMCOG, Cambridge Subscale of CAMDEX, assesses orientation, language, memory, praxis, attention, abstract thinking, perception and calculation (includes MMSE); Stroop, Stroop Color-word Test; po, orally; IM, intramuscular; IV, intravenous

[a] 4 wk of treatment were followed by 3 mo follow-up without treatment; results are reported at baseline and at the end of 3 mo follow-up.
[b] 1 mg weekly for 4 weeks.
[c] ANOVA, comparing all 3 groups simultaneously.
[d] 136-203 pg/mL.
[e] 1 mg 3x in week 1, then 1/week x 3 weeks, then 1/month.
[f] <163 pg/mL.
[g] 100 µg x 5 times /wk x 14 wk.

Table 12. Effect of vitamin B12 intervention on cognitive function tests in non-randomized trials

Author Year	Duration	Intervention: Dose mg/day	Intervention: Route	N	Test /Subtest	Maximum Score	Base value	Change: Value	Change: *P value* Change	Population	Mean Age (yr)	Applicability	Quality
Non-randomized comparative trial													
van Asselt, 2001	5 mo	1	IM	16	MMSE ↑	nd		No change		Normal Low serum B12 [b]	71	👫	C
		1/wk [a]	IM	16	Forward & Backward Digit Span ↑ (WAIS-R)	nd		No change					
		1/wk [a]	IM	16	Verbal Word Learning Test ↑ (Delayed recall)	nd	6	+5 +1	0.03				
		1/wk [a]	IM	16	Verbal Fluency ↑	nd	20	-2 -5	0.03				
		1/wk [a]	IM	16	Similarities ↑	nd	7	0 -2	0.04				
		1/wk [a]	IM	16	Trail Making Test ↑	nd		No change					
		1/wk [a]	IM	16	Rivermead Behavioral Face Recognition Test ↑	nd		No change					
Cohort studies													
Ito, 2001	4 wk	1.5 – 3 [c]	nd	14	MMSE ↑	30	10.1	+0.3	NS	AD [d]	78	👫	C
		1.5 – 3 [c]	nd	6	MMSE ↑	30	17.3	+0.4	NS	Questionable or mild AD [d]	78		
		1.5 – 3 [c]	nd	8	MMSE ↑	30	4.8	+0.1	NS	Moderate or severe AD [d]	78		
Teunisse, 1996	6 mo	1 [e]	IM	19	MMSE ↑	30	17.5	-1.8	<0.05	Dementia Low serum B12 [f]	76	👫	C

Continued

Table 12. Effect of vitamin B12 intervention on cognitive function tests in non-randomized trials (Continued)

Author Year	Duration	Intervention		N	Test /Subtest	Maximum Score	Base value	Change		Population	Mean Age (yr)	Applicability	Quality
		Dose mg/day	Route					Value	*P value* Change				
Abyad, 2002	12 mo	1/mo [g]	IV	56	MMSE ↑	30	14.5	+0.5	nd	Dementia Low serum B12 [h]	82		C
		1/mo [g]	IV	22	MMSE ↑	30	19	+6	.007	Dementia (Short-term Tx) Low serum B12 [h]	82		
		1/mo [g]	IV	34	MMSE ↑	30	18	+4	NS	Dementia (Long-term Tx) Low serum B12 [h]	82		
Ikeda, 1992	8 wk [j]	1.5/wk [k]	IV	19	MMSE ↑	30	20 [L]	+1	NS	AD	71		C
		1.5/wk [k]	IV	19	Mattis' DRS ↑	150	112 [L]	+3	<.05				
Martin, 1992	>7 mo	1/mo [m]	IM	13	Mattis' DRS ↑	144	108	-3	NS	Cognitive impairment (long duration) Low serum B12 [n]	79		C
		1/mo [m]	IM	5	Mattis' DRS ↑	144	108	+20	.008	Cognitive impairment (short duration) Low serum B12 [n]			
Mitsuyama, 1988	2 mo	2 + 0.5	po + IM	9	GBS ↑	nd	Improvement from baseline [o]			Dementia	53		C
		2	po	5	GBS ↑	nd	No change from baseline [o]						
Ikeda, 1992	8 wk [j]	1.5/wk [k]	IV	19	GBS ↑	nd	90	-10 [L]	<0.05	AD	71		C
Teunisse, 1996	6 mo	1 [e]	IM	19	CAMCOG ↑	106	64.9	-1.4	NS	Dementia Low serum B12 [f]	76		C
		1 [e]	IM	19	IDDD-Initiative ↑	36	13.8	-4.9	<0.05				
		1 [e]	IM	19	IDDD-Performance ↑	44	12.7	-7.8	<0.05				
		1 [e]	IM	19	RMBPC-Memory ↑	28	17.5	-0.4	NS				
		1 [e]	IM	19	RMBPC-Disruptive behavior ↑	32	4.4	-2.6	<0.05				
Ikeda, 1992	8 wk [j]	1.5/wk [k]	IV	19	HDS ↑	nd	28	+5 [L]	<0.05	AD	71		C
Carmel, 1995	6-8 mo	1/wk [p]	IM	14	CERAD ↑	nd	Improvement: 1 subject [q] No change: 12 subjects [q] Worse: 1 subject [q]			AD, Dementia Low serum B12 [r]	71		C

↑ Higher score indicates better cognitive function. ↓ Lower score indicates better cognitive function. CAMCOG, Cambridge Subscale of CAMDEX, assesses orientation, language, memory, praxis, attention, abstract thinking, perception and calculation (includes MMSE); MMSE, mini-mental status examination; IDDD, Interview for Deterioration in Daily living activities in Dementia, caregiver assessment of functioning in the past week; subscales for initiative and performance; RMBPC, Revised Memory and Behavioral Problems; 3 subscales for memory, depression (not included here), and disruptive behavior; CERAD battery includes MMSE, 15-item naming task, verbal fluency task, verbal memory task, visuoconstructive task; GBS, Gottfries-Brane-Steen scale; HDS, Hasegawa's Dementia Rating Scale; WAIS-R, Wechsler Adult Intelligence Scale - Revised; Mattis' DRS, Mattis' Dementia Rating Scale.

[a] 1 mg weekly x 4 weeks, then monthly x 4 months.
[b] ≤ 203 mg/mL.
[c] 1.5 mg/day x 2 weeks, then 3.0 mg/day x 2 weeks.
[d] Dementia of Alzheimer's Type (DAT); Clinical Dementia Rating (questionable dementia 0.5 points, mild 1, moderate 2, severe 3).
[e] 1 mg/day x 5 days, then per month, or 1mg/week x 5 weeks, then bi-monthly.
[f] <200 pg/mL.
[g] 1 mg IV daily for 1 week; then weekly for 1 month; then monthly thereafter.
[h] <300 pg/mL.
[j] There is also follow-up for 4 months after treatment completion: NS results compared to baseline were reported at the end of that period.
[k] 500 µg 3x/week x 8 weeks.
[L] Results are presented graphically.
[m] 1 mg/day for 1 week, weekly for 1 month, then monthly ≥6 months.
[n] <203 pg/mL.
[o] Results not reported.
[p] 1 mg weekly for 8 weeks, then monthly for ≥4 months.
[q] Results on CERAD scores are not reported.
[r] <190 pg/mL.

Folate Intervention Studies

Study Descriptions. Three RCTs[65,79,80] and two uncontrolled cohort studies[81,82] reported data on folate supplementation and the effect on cognitive function or therapeutic benefit. Two studies were conducted among subjects with dementia, one among cognitive impaired, one among normal subjects, and the fifth among those with PD. All but one study included subjects whose mean ages were 60 years and above; the remaining study did not document mean age. The studies tested various doses of folic acid or folate ranging from 0.75 to 20 mg daily. These doses are all substantially larger than the US RDA of 0.4 to 1 mg per day. Study durations ranged from 5 to 17 weeks. The primary outcome for three studies was cognitive function measured with WAIS-R and/or other cognitive tests. One study also evaluated therapeutic benefit. About 130 subjects were tested in five studies. All studies were of moderate to poor quality (2 B, 3 C). Three studies have moderate, and two narrow applicability.

Overall Effect. Among the five studies that measured cognitive function in people with dementia, cognitive impairment, or no disease, one RCT found a trend towards worsening of neuropsychological scores in the folic acid treatment group, suggesting a negative benefit of high dose folate among subjects with dementia. Two other studies, one RCT and one uncontrolled cohort studies found statistically significant improvement with folic acid or folate treatment compared with placebo among demented, cognitive impaired, and normal subjects, but did not report any clinical benefit. The study of patients with PD found no therapeutic benefit.

Fioravanti 1997 compared the effects of folic acid intervention with placebo among cognitively impaired subjects who had serum folate levels below 3 ng/mL. Cognitive function was assessed using six components of the Randt Memory Test (RMT). Compared to baseline the folic acid treatment group showed significant improvement in Attention Efficiency score, one of the six components of RMT, after 60 days treatment. However comparison between folic acid and placebo groups showed significant changes in the actively treated group with improvement in four out of six cognitive components of RMT.

Bryan 2002 was a double blind, placebo controlled randomized trial conducted to assess the effect of vitamin supplementation and dietary intake among normal women. The study utilized a mixed factorial design with four treatment groups (B6, B12, folate, and placebo) and three age

groups (younger, middle-aged, and older) to assess the effect on cognitive performance. Here we summarize the results from the subgroup of older women who were treated with a small dose of folate (0.75 mg). In post hoc comparisons of two measures of memory, Rey Auditory-Verbal Learning Test (RAVLT) immediate recall and recognition list, and verbal ability (verbal fluency-initial letter), older women in the folate treatment group identified significantly more words when compared to the placebo group. No significant effect was observed in other tests.

Sommer 2003, in a very small double blind RCT, compared 20 mg per day of folic acid to placebo in seven subjects who fulfilled the standard diagnostic criteria for dementia. There were small trends towards a negative effect on cognitive abilities with folic acid treatment in two of the cognitive tests, the Associated Learning subtest that measures verbal learning, and Trails B that measures perpetual motor speed.

Rapin 1988 recruited subjects with dementia and low red blood cell (RBC) folate levels. This study was an uncontrolled cohort study that treated dementia subjects with 50 mg per week of folinic acid for about 17 weeks. Treated subjects had a significantly improved performance in five of 16 cognitive tests. They also reported improved feeling of well-being.

The single study of patients with PD, by McGeer 1972, was a cohort study of 15 mg per day of folic acid among 18 subjects. The study found that the folic acid intervention provided slight to no therapeutic benefit assessed by subjective or objective change in PD symptoms.

Interactions and Covariates. The intervention trials did not provide adequate evidence to support any dose effect of folate on the outcomes. However, Fioravanti 1997 found that the cognitive improvement after folate intervention was correlated in a linear fashion with the low levels of folate at baseline. One RCT[80] and one uncontrolled study[82] studied the effect of folic acid intervention on cognitive function among subjects with low serum or RBC folate levels, and one RCT among those with normal folate levels.[79]. Two other studies did not provide data on blood folate levels before or after intervention. One RCT and one uncontrolled cohort study reported significant effects in the same cognitive domain.

Summary. A total of five studies of moderate to poor quality reported data on the effect of folate intervention among normal people or those with dementia, cognitive impairment, or PD. Overall, one RCT among subjects with dementia and normal folate levels found a trend towards worse performance in the cognitive function scores with folic acid intervention. Two studies, one RCT and one uncontrolled cohort study found statistically significant improvements in the cognitive scores in the actively treated groups among demented, cognitive impaired, and normal subjects and the last found no benefit among PD subjects. However, interpretation of the cohort studies is difficult without a comparable control group given the variable course of dementia over time. None of the studies provided data on clinically significant effect after the vitamin intervention.

Table 13. Effect of folic acid or folate intervention on cognitive function tests

Design Author Year	Duration	Intervention Dose mg/day Control	Route	N	Test /Subtest	Maximum Score	Base value	Change Value	Change *P value* Change	Net Change Value	Net Change *P* value Net Change	Population	Mean Age (yr)	Applicability	Quality
RCT															
WAIS-R															
Bryan 2002	5 wk	0.75	po	75 nd	Digit Symbol Coding (120 s) ↑	nd	62.5	+6.9	nd	*+2.1*	*NS*	Normal	74		B
		Placebo					62.3	+4.8							
		0.75	po	75 nd	Digit span - Backwards ↑	nd	6.7	+1.7	nd	*+1.3*	*NS*				
		Placebo					7.1	+0.4							
Sommer 2003	10 wk	20	po	43	Wechsler Memory Scale ↑ - Logical Memory Subtest	nd	4.9	0	nd	*-1.7*	*NS*	Dementia Normal folate	77		C
		Placebo					4.6	+1.7							
		20	po	43	Wechsler Memory Scale ↑ - Associate Learning Subtest	nd	16.6	-7.8	nd	*-7.5*	*.08*				
		Placebo					11.0	+0.3							
		20	po	43	Pro-rated Verbal IQ (WAIS-R) ↑	nd	107.8	-2.5	nd	*+10.0*	*NS*				
		Placebo					110.0	+12.5							
Miscellaneous															
Fioravanti 1997	60 d	15	po	16 14	Acquisition & recall [a] ↑	nd	55.3	+4.2	nd	*+5.5*	*<0.007*	Cognitive impaired Low folate [b]	80		B
		Placebo					62.1	-1.2							
		15	po	16 14	Delayed recall [a] ↑	nd	56.1	+7.4	nd	*+7.4*	*<0.007*				
		Placebo					63.0	0							
		15	po	16 14	Memory index [a] ↑	nd	49.3	+6.8	nd	*+6.3*	*<0.002*				
		Placebo					57.1	0.5							
		15	po	16 14	Encoding [a] ↑	nd	4.3	+0.5	nd	*+0.7*	*<0.005*				
		Placebo					5.3	-0.2							
		15	po	16 14	Cognitive efficiency [a] ↑	nd	3.28	+0.63	nd	*+0.57*	*NS*				
		Placebo					4.25	+0.06							
		15	po	16 14	Attention efficiency [a] ↑	nd	6.40	+1.12	*<0.05*	*+0.97*	*NS*				
		Placebo					6.83	+0.07	NS						
Bryan 2002	5 wk	0.75	po	75 nd	Executive function Stroop ↑	nd	2.50	-0.03	nd	*+0.09*	*NS*	Normal	74		B
		Placebo					2.51	-0.12							
		0.75	po	75	Verbal fluency: Initial letter ↑	nd	29.3	-0.1	nd	*-3.4*	*NS*				

Design Author Year	Duration	Intervention Dose mg/day Control	Route	N	Test /Subtest	Maximum Score	Base value	Change Value	*P value* Change	Net Change Value	*P* value Net Change	Population	Mean Age (yr)	Applicability	Quality
		Placebo		nd			23.7	+3.3							
		0.75	po	75	Verbal ability - Vocabulary ↑	nd	23.3	-0.3	nd	*-0.1*	*NS*				
		Placebo		nd			21.9	-0.1							
Sommer 2003	10 wk	20	po	4	Boston Naming Test ↑	nd	40.8	+1.2	nd	*-0.2*	*NS*	Dementia Normal folate	77	♂	C
		Placebo		3			42.3	+1.4							
		20	po	4	Controlled Oral Word Association Test ↑	nd	29.5	+3.3	nd	*+8.3*	*NS*				
		Placebo		3			36.0	-5.0							
		20	po	4	Speed/Concentration: Trails A ↑	nd	233.0	+14.8	nd	*+31.5*	*NS*				
		Placebo		3			277.7	-16.7							
		20	po	4	Speed/Concentration: Trails B ↑	nd	373.0	+20.3	nd	*+75.0*	*.08*				
		Placebo		3			412.0	-54.7							
		20	po	4	Speed/Concentration: Finger Tapping Test ↑	nd	38.4	-1.5	nd	*+6.9*	*NS*				
		Placebo		3			32.7	-8.4							

Continued

Table 13. Effect of folic acid or folate intervention on cognitive function tests (Continued)

Design		Intervention Dose mg/day Control	Route	N	Test /Subtest	Maximum Score	Base value	Change Value	Change *P value*	Net Change Value	Net Change *P* value	Population	Mean Age (yr) Applicability Quality
Author Year	**Duration**												
Cohort													
McGeer 1972	45 d	15	po	18	Therapeutic benefit		33% No therapeutic benefit 61%: Slight subjective benefit, no objective change 5%: Worsening of gait.					PD	nd 🚻 C
Rapin 1988	120 d	~7 [c]	po	38	Battery of cognitive tests		Significant improvement in 5 of 16 tests, including tests of visuo-spatial memory and organization, associative memory, and logical reasoning. No change in 11 other tests.					Dementia Low folate [d]	62 🚻 C

⭱ Higher score indicates better cognitive function. ⭳ Lower score indicates better cognitive function. d: days; N: number; NS: non-significant; nd: not documented; po, orally; wk: week; WAIS-R, Wechsler Adult Intelligence Scale-Revised

[a] Part of Randt Memory Test.
[b] <3 ng/mL.
[c] Folinic acid 50 mg/week.
[d] RBC folate <300 ng/mL.

Combined B Vitamins Intervention Studies

Study Descriptions. Six studies, including 3 RCTs[83-85] and 3 uncontrolled cohort studies[86-88] assessed the effects of a combination of B vitamins as interventions on cognitive function in elderly subjects. Four trials included subjects with AD and/or mixed dementia,[83,85,86,88] one with cognitive impairment,[87] and one without dementia.[84] All studies used different daily doses of various B vitamins in the ranges of 0.8 to 15 mg folic acid or folate, 3 to 80 mg B6, and 0.1 to 2 mg B12; all substantially over the US RDA. Three used a combination of folic acid , B6, and B12, two used folic acid and B12, and one used folate and B12. All but one study treated subjects with oral vitamin supplementation; Shaw 1971 used a combination of B12 injection and oral folate. All studies included subjects whose mean ages were greater than 70 years. The primary outcome for all studies was cognitive function. About 470 subjects were tested in six studies. All studies were of moderate to poor quality (2 B, 4 C). One study has broad applicability, four moderate, and two narrow applicability.

Overall Effect. Five of the six studies found no significant change in cognitive function, generally measured with MMSE or WAIS, after combination B vitamin supplementation.

The single study to find a significant improvement, Nilsson 2001, was an uncontrolled cohort study. This study found significant changes in the cognitive score performance among subjects with mild-moderate dementia and elevated plasma homocysteine concentration with a significant global clinical improvement after vitamin intervention. There was a four point increase in the mean MMSE score from a baseline score of 17. However the same study failed to show any improvement among patients with severe dementia or those with mild-moderate dementia and normal plasma homocysteine levels with a mean baseline score of 21 after combined vitamin intervention.

Lewerin 2005, a RCT, compared moderate doses of vitamins supplementation to placebo among ambulatory normal subjects, and measured cognitive function with a battery of nine tests. The placebo arm performed better in three of the tests compared to the actively treated group. Two other RCTs reported no significant changes in cognitive function in either intervention arms after vitamin supplementation. The remaining two cohort studies, Aisen 2003 and Lehmann 2003, reported no observable differences after treatment.

Interactions and Covariates. There was no dose related responses discussed in the studies. Only Nilsson 2001, an uncontrolled cohort study reported a difference in cognitive function with relation to severity of dementia, and with the levels of plasma homocysteine (<2.69 versus >2.69 mg/L) after combined B vitamin intervention. This study also reported a significant improvement in alertness, orientation in time and space, recent memory and fewer clinical fluctuations among subjects with dementia after combined vitamin intervention. One RCT[85] used a combination of B12 injection and oral folate among senile dementia with high and low RBC folate levels; remainder of the studies evaluated combined vitamin intervention among those with normal blood vitamin levels. There was no evidence across studies of differences in effect on tests of different cognitive domains.

Summary. Six studies of moderate to poor quality reported data on the effect of combined B vitamin intervention among normal people, cognitively impaired, and those with AD and/or mixed dementia. The three RCTs found no benefit in the actively treated arm compared to placebo. Only one of the uncontrolled cohort studies found both statistically and clinically significant large benefit. However, interpretation of the cohort studies is difficult without a comparable control group given the variable course of dementia over time. The two other uncontrolled cohort studies reported no benefit after intervention.

Table 14. Effect of combination B vitamin interventions on cognitive function

Design		Intervention Dose/day																			
		Control												Change		Net Change					
Author Year	Duration	B1 (g)	B2 (mg)	Folate mg)	B6 (mg)	B12 (mg)	Route	N	Test /Subtest	Maximum Score	Base value	Value	*P value* Change	Value	*P value* Net Change	Population	Mean Age (yr) Applicability Quality
RCT																					
Clarke 2003	12 wk			2		1	po	74	MMSE ↑	30	21	nd	NS			Dementia	75	B
			Placebo					75													
				2		1	po	74	ADAS ↓	70	27	nd	NS								
			Placebo					75													
Leweri n 2005	4 mo			0.8	3	0.5	po	115	Digit Span Forward (WAIS) ↑	9	5.8	+0.2	.09	*-0.1*	NS	Normal	76	B
			Placebo					64			5.9	+0.3	NS								
				0.8	3	0.5	po	115	Digit Span Backward (WAIS) ↑	8	4.4	+0.25	.09	*+0.03*	NS						
			Placebo					64			4.6	+0.22	NS								
				0.8	3	0.5	po	114	Block Design (WAIS) ↑	42	18.5	+1.0	NS	*+0.2*	NS						
			Placebo					61			20.0	+0.8	NS								
				0.8	3	0.5	po	113	Digit Symbol (WAIS) ↑	90	35.1	+0.9	NS	*-1.4*	.09 [a]						
			Placebo					62			38.0	+2.3	NS								
				0.8	3	0.5	po	115	Identical Forms ↑	60	23.3	+0.1	NS	*-1.4*	.04 [a]						
			Placebo					61			24.8	+1.5	NS								
				0.8	3	0.5	po	113	Visual Reproduction ↑	14	6.9	+0.6	NS	*0*	NS						
			Placebo					62			7.0	+0.6	NS								
				0.8	3	0.5	po	110	Synonyms ↑	30	22.5	+0.31	NS	*-1.0*	.02 [a]						
			Placebo					61			22.4	+1.3	NS								
				0.8	3	0.5	po	115	Thurstone's Picture Memory Test ↑	28	20.3	+1.7	NS	*-1.7*	NS						
			Placebo					63			21.1	+2.4	NS								
				0.8	3	0.5	po	113	Figure Classification ↑	30	15.8	+1.5	NS	*+0.9*	NS						
			Placebo					62			16.8	+0.6	NS								

Design		Intervention Dose/day																	
		Control										Change		Net Change					
Author Year	Duration	B1 (g)	B2 (mg)	Folate mg)	B6 (mg)	B12 (mg)	Route	N	Test /Subtest	Maximum Score Base value	Value	*P value* Change	Value	*P* value Net Change	Population	Mean Age (yr)	Applicability	Quality
Shaw 1971	12 wk			15		1 [b]	po IM	17	Dementia Scale ↑		The means were unchanged in both groups				Severe Dementia High folate and low folate	81	♂	C
	Placebo																	
	12 wk			15		1 [b]	po IM	17	Blessed Information-Memory Concentration Test ↑		Mild increase, not statistically significant							
	Placebo																	

Continued

Table 14. Effect of combination B vitamin interventions on cognitive function (Continued)

Design		Intervention Dose/day										Change		Net Change					
Author Year	Duration	Control B1 (g)	B2 (mg)	Folate mg)	B6 (mg)	B12 (mg)	Route	N	Test /Subtest	Maximum Score	Base value	Value	*P value* Change	Value	*P* value Net Change	Population	Mean Age (yr)	Applicability	Quality
Cohort																			
Aisen 2003	8 wk			5	50	1	po	63	MMSE ⭱	30	19.2	+0.1	NS			AD	71	🚻	C
Nilsson 2001	2 mo			5		1	po	11	MMSE ⭱	30	21.3	-0.4	NS			Mixed Dementia Hcy <2.69 mg/L	78	🚻	C
		Placebo						17			17.2	+4.2	<.01			Mixed Dementia Hcy >2.69 mg/L			
				5		1	po	11	SKT ⭳	27	15.6	-0.8	NS			Mixed Dementia Hcy <2.69 mg/L			
		Placebo						17			18.5	-3.9	<.01			Mixed Dementia Hcy >2.69 mg/L			
Lehmann 2003 [c]	270 d [d]			10	80	2	po	30	MMSE ⭱	30	26.3	+0.1	NS			Mild cognitive impairment	72	🚻	C
									CSF-tau		529	-39	NS						

⭱ Higher score indicates better cognitive function. ⭳ Lower score indicates better cognitive function. CSF: cerebrospinal fluid; d: days; Hcy: homocysteine; IM; intramuscular; MMSE, mini mental status examination; nd: not documented; NS: non-significant; po, orally; SKT: a short cognitive test for assessing memory and attention; WAIS: Wechsler Adult Intelligence Scale

[a] Placebo better than B vitamin.
[b] B12 injections of hydroxycobalamin 1000 mg daily for 1st week and weekly for 11 weeks thereafter.
[c] Used 35 healthy controls for CSF tau; no data documented for controls.
[d] Mean. Range = 110-740 days.

Association of Dietary Intake Levels of B Vitamins to Age-Related Neurodegenerative Diseases

In this section, we summarize the findings from five (retrospective and prospective) longitudinal studies[89-91] and five cross-sectional studies[65,92-96] that examined the association between the dietary intake levels of B vitamins and cognitive function or the risk of age-related neurodegenerative diseases. We included all populations from longitudinal studies, while only non-institutionalized or free-living populations were included from cross-sectional studies in order to assess their "usual" dietary intake levels. All dietary assessment methods have certain strengths and limitations; thus it is important to choose an appropriate method depending on the study design and research questions.[97] For example, a food record or diet recall is appropriate for estimating the mean dietary intakes in the study population. Food frequency questionnaire (FFQ) is a semi-quantitative instrument and it is designed to estimate the long-term usual intake. FFQ is good for ranking subjects' intake levels, but might not be appropriate for estimating the mean dietary intake levels.

Longitudinal Studies

Study Descriptions. One prospective nested case-control study, three prospective cohort studies, and one retrospective case-control study examined the association between dietary intake levels of B vitamins and neurodegenerative diseases or cognitive function (Tables 15-17). Each study associated the B vitamin intake levels with different outcomes, including the risk of newly developed PD cases, rates of cognitive change per year, follow-up cognitive function examined by various cognitive tests, and a diagnosis of probable AD. Two studies were of good quality, one study was of moderate quality, and the other two studies were of poor quality.

Overall Effects. Chen 2004 conducted a nested case-control study to investigate whether intake of folate or related B vitamins involved in folate and homocysteine metabolism was associated with PD risk, using two large cohorts in the US – the Health Professionals Follow-up study (1986-2000) and the Nurse's Health Study (1980-1998).[89] The two cohorts were analyzed separately and then pooled analyses were also performed. Participants' dietary intakes were assessed by a food frequency questionnaire during the previous 12 months. It was found that controlling for age, smoking, alcohol consumption, caffeine intake and lactose intake, there were no significant associations found between the baseline intake of folate, vitamin B6, or vitamin B12 and relative risk of PD in either study. Several sensitivity analyses were also performed for different levels of folate intake. Individuals at either the low end (≤200 μg/day) or the high end (>1000 μg/day) of folate intake had a PD risk similar to that of people with normal folate intake, controlling for various possible confounders. Furthermore, in a separate analysis, supplemental intake of folate, vitamin B6, or vitamin B12 was also not related to the risk of PD. Compared with non-supplemented participants, individuals whose supplemental folate intake was more than 400 μg per day had a pooled RR of 1.0.

Morris 2005 conducted a prospective longitudinal cohort study to examine the associations of dietary folate and vitamin B12 with 6-year cognitive change in the participants of the Chicago Health and Aging Project.[98] Change in cognitive function measured at baseline, 3-year and 6-year follow-ups, using the average z score of four tests: the East Boston Tests of immediate and delayed recall, the Mini-Mental State Examination, and the Symbol Digit Modalities Test. The

median dietary intake of folate ranged from 175 to 382 µg/day for first and last quintile respectively. The median intake of folate, from food and supplements, ranged from 186 to 742 µg/day for first and last quintile respectively. At baseline, it was found that persons with high intake of total folate (from food and supplements) tended to have a more favorable risk profile for cognitive change (more years of education, higher baseline cognitive scores, and greater consumption of vitamin E and vitamin C) than persons with low intake. After a median follow-up of 5.5 years, unexpectedly, high folate intake from food sources and/or supplements was associated with a faster rate of cognitive decline in a mixed models adjusted for multiple risk factors. Further sensitivity analyses showed no change in the effect estimates after restricting the analyses in persons who reported poor health status or with low baseline cognitive scores (bottom 15% of the distribution) at baseline. Intake of vitamin B12, with or without vitamin supplementation, was not significantly associated with cognitive change in the multivariate model or with adjustment for folate intake (data not shown).

Part of Tucker 2005 study examined the association between dietary B6, B12 and folate intakes and 3-year changes in cognitive measures in the Veterans Affairs Normative Aging, a longitudinal cohort consists of 321 aging men at baseline.[96] Cognitive function was assessed with the MMSE and on the basis of measures of memory, verbal fluency, and constructional praxis, which were adapted from the revised WAIS and the CERAD batteries at 2 time points. Improbable dietary intakes (total energy >16.75 or <2.51 MJ) were excluded from further analysis. Over a mean 3-year follow-up, changes in constructional praxis measured by spatial copying were significantly associated with dietary folate, B6 and B12. The mean dietary folate, B6 and B12 was 440 µg/day, 3.98 mg/day and 9.57 µg/day, respectively. Dietary folate remained independently protective against a decline in spatial copying score after adjustment for other vitamins and for plasma homocysteine. Dietary folate was also protective against a decline in verbal fluency. There was no other significant association found between dietary folate, B6, or B12 and changes in other cognitive measures. The major limitation of these analyses is that dependent biases might occur, since the dietary intakes and cognitive measures were both assessed by self-administered instruments.

Deijen 2003 conducted a prospective cohort study to examine the relation between nutritional intake and daily functioning in elderly people being evaluated in a psychogeriatric nursing home.[90] During the study 60 percent of the dropouts "became ill" compared to 34 percent of the subjects who completed the study. Participants' dietary intakes were assessed by a combination of a 3-day record and weighing-back methods at baseline, weeks 8, 16 and 24, recorded by nurses. An analysis was performed to test for associations with change in ZIG-scores. Two experimental groups were formed based on high (>1.0 mg/day) and low intakes (≤1.0 mg/day) of B6 compared to their median intakes at baseline. There were no interactions between intake groups and week, indicating that the high and low intake groups had the same pattern of ZIG-scores across the 6-month experimental period. There was deterioration in cognitive, physical and social functioning with time. However, this study had several limitations. Dropouts had worse health status than completers; it is unclear whether the nurses who assessed exposure and outcomes were the same; and the restriction to nursing home residents limits applicability.

Mizrahi 2003 conducted a retrospective case-control study compared patients with AD to healthy controls.(Mizrahi, 2003 2188 /id} Both proxy and surrogate respondents of cases and controls were asked to recall their food consumptions using a food frequency questionnaire during three age periods: 20 to 39, 40 to 59 and 60 or more years old. It was found that those with AD had lower mean dietary vitamin B6 and folate intake compared to controls in the over

60 years of age period (P=0.05 and 0.01, respectively), but not in younger age periods. No statistically significant correlations were found between homocysteine levels and dietary vitamin B6 and folate intake in the three age periods for those with AD and controls. This study was deemed to be of poor quality due to serious recall biases. Specifically, controls might have had more accurate recalls than cases, because cases' intakes were estimated by proxy or surrogate respondents, and all respondents might remember the food consumption during more recent age period better than distant age periods. Finally, the recall periods were too long to obtain accurate food consumption data.

Summary. No significant associations were found between dietary intakes of B6 or B12 and PD, AD, cognitive functioning, or cognitive decline across three studies. One additional study found higher dietary intakes of B6, B12, and folate were associated with improvements in some, but not all, cognitive function measures. In three separate studies, folate intake was not associated with PD or AD; however, in one study, higher folate intake from food sources and/or supplements was associated with a faster rate of cognitive decline after adjusting for multiple risk factors.

Table 15. Association between dietary intake levels of vitamin B6 and neurodegenerative diseases or cognitive function in longitudinal studies

Author Year Country	Baseline Population	Baseline Mean Age (yr)	N	Study Design (Follow-up Duration)	Dietary Assessment Method	Outcomes	Mean Daily Intake (mg/day)		Results: RR /OR, β[i]	Results: P_{btw} / (95%CI)	Results: P_{trend}	Applicability	Quality
Chen, 2004 US	Normal, all	30-75	136,057	Prospective nested case-control study (Mean follow-up 12.7 yr in men & 17.3 yr in women)	Food frequency questionnaire, validated	Risk of newly developed PD cases analyzed by Cox proportional hazard models	Quintile 1	nd	1.0[b]	Ref	NS	🧍🧍🧍	A
							Quintile 2	nd	1.1	(0.8, 1.6)			
							Quintile 3	nd	1.3	(0.9, 1.0)			
							Quintile 4	nd	0.9	(0.7, 1.3)			
							Quintile 5	nd	1.0	(0.7, 1.4)			
	Normal, men	40-75	47,341				Quintile 1	3.6[a]	1.0[b]	Ref	NS		
							Quintile 2	4.3[a]	1.3	(0.8, 2.0)			
							Quintile 3	5.6[a]	1.3	(0.9, 2.0)			
							Quintile 4	7.9[a]	0.8	(0.5, 1.3)			
							Quintile 5	22.1[a]	1.0	(0.6, 1.6)			
	Normal, women	30-55	88,716				Quintile 1	1.6[a]	1.0[b]	Ref	NS		
							Quintile 2	1.9[a]	0.9	(0.5, 1.6)			
							Quintile 3	2.3[a]	1.4	(0.8, 2.3)			
							Quintile 4	3.3[a]	1.1	(0.7, 1.9)			
							Quintile 5	5.8[a]	1.1	(0.7, 1.4)			
Tucker, 2005	Normal, men	67	241-287	Prospective longitudinal cohort study (mean 3 yr)	Food frequency questionnaire, validated	Constructional praxis: spatial copying, sum of drawings	4.0 ± 7.2 SD (range 0.5-85.5) (N=321)		0.30[j]	<.05	--	🧍🧍	B
						Language: verbal fluency, no. correct			0.81[j]	<.10	--		
						Working memory: backward digit span, longest span recalled			0.04[j]	NS	--		
						Recall memory: word lists, total of 3 trials			0.21[j]	NS	--		
						Mini-Mental State Examination			-0.05[j]	NS	--		
Deijen, 2003 Netherlands	Mixed	83	90	Prospective cohort study (6 mo)	3-day food records, weighing food	Zorg Index Geriatrie (ZIG)-scales[f] ↓	Low intake	≤1.0[g]	nd	NS[h]	Diet: NS; ZIG: <.0005[i]	🧍🧍	C
							High intake	>1.0[g]					

Continued

Table 15 Association between dietary intake levels of vitamin B6 and neurodegenerative diseases or cognitive function in longitudinal studies (Continued)

Author Year Country	Baseline Population	Baseline Mean Age (yr)	N	Study Design (Follow-up Duration)	Dietary Assessment Method	Outcomes	Mean Daily Intake (mg/day)		Results: RR /OR, β[i]	Results: P_{btw} / *(95%CI)*	Results: P_{trend}	Applicability	Quality
Mizrahi, 2003 US	AD[f]	74	<64[c]	Retrospective case-control study (3 age periods: 20-39, 40-59; 60+ yr old)	Food frequency questionnaire	Diagnosis of probable AD, fulfilling NINCDS/ADRDA criteria	20-39 yr	0.90[d]	nd	NS[e]	nd	↟↟↟	C
							40-59 yr	0.90[d]		NS[e]			
							60+ yr	0.96[d]		.05[e]			
	Normal	75	<64[c]				20-39 yr	0.90[d]	nd	Ref	nd		
							40-59 yr	0.95[d]		Ref			
							60+ yr	1.10[d]		Ref			

↡ Lower score indicates better cognitive function. Ref=reference group for comparisons

[a] Median intake
[b] All RRs were adjusting for age, smoking, total energy intake, alcohol consumption, caffeine intake, and lactose intake
[c] Missing data on dietary intake for some of the participants resulted in different sample sizes for the various time periods
[d] Values were estimated from graphs. Intake amount is per 1000 Kcal
[e] Two-sample t-tests were used to compare the mean levels of dietary folate or vitamin B6 for AD patients and controls (reference group) at 3 age periods separately. These analyses were not adjusted for any confounders
[f] The ZIG-scale consists of ZIG-A scale (cognitive functioning), ZIG-B scale (social functioning) and the ZIG-C scale (social functioning). The ranges of the ZIG-scales are from 6 to 24. The higher the score, the worse the outcome. For the purpose of this review, we only look at the results of ZIG-A scale.
[g] Mean intake was averaged for each subject across the 12 assessments: 3 across 1 week, 4 across 24 weeks
[h] Repeated measurements analyses were carried out with ZIG-scores as repeated measurement factor and 3 comparisons were separately made between low/high intake groups of vitamin B6 as between subjects factor
[i] Slope for the multivariate linear regression model
[j] Final cognitive measures regressed onto baseline diet, adjusted for baseline cognitive measures, age, education, smoking, alcohol intake, BMI, diabetes (yes or no), systolic blood pressure, time of second measure relative to folic acid fortification, time interval between the 2 cognitive measures, and total energy intake. All outcomes and dietary intake measures were log-transformed.

Table 16. Association between dietary intake levels of vitamin B12 and neurodegenerative diseases or cognitive function in longitudinal studies

Author Year Country	Baseline Population	Baseline Mean Age (yr)	N	Study Design (Follow-up Duration)	Dietary Assessment Method	Outcomes	Mean Daily Intake (µg/day)		Results: RR /OR, β[d]	Results: P_{btw} / (95%CI)	Results: P_{trend}	Applicability	Quality
Chen, 2004 US	Normal, all	30-75	136,057	Prospective nested case-control study (Mean 12.7 yr in men & 17.3 yr in women)	Food frequency questionnaire, validated	Risk of newly developed PD cases analyzed by Cox proportional hazard models	Quintile 1	nd	1.0[b]	Ref	NS	🚹🚹🚹	A
							Quintile 2	nd	1.2	(0.9, 1.6)			
							Quintile 3	nd	1.0	(0.7, 1.4)			
							Quintile 4	nd	0.9	(0.7, 1.3)			
							Quintile 5	nd	1.0	(0.7, 1.4)			
	Normal, men	40-75	47,341				Quintile 1	8.6[a]	1.0[b]	Ref	NS		
							Quintile 2	9.4[a]	1.1	(0.7, 1.6)			
							Quintile 3	10.4[a]	0.8	(0.5, 1.2)			
							Quintile 4	13.1[a]	0.9	(0.6, 1.3)			
							Quintile 5	21.9[a]	1.0	(0.7, 1.4)			
	Normal, women	30-55	88,716				Quintile 1	5.5[a]	1.0[b]	Ref	NS		
							Quintile 2	6.1[a]	1.5	(0.9, 2.5)			
							Quintile 3	6.8[a]	1.5	(0.9, 2.4)			
							Quintile 4	9.2[a]	1.0	(0.6, 1.7)			
							Quintile 5	17.1[a]	1.0	(0.6, 1.7)			
Tucker, 2005	Normal, men	67	241-287	Prospective longitudinal cohort study (mean 3 yr)	Food frequency questionnaire, validated	Constructional praxis: spatial copying, sum of drawings	9.6 ± 5.7 SD (range 1.4-57.0) (N=321)		0.37[c]	<.05	--	🚹🚹	B
						Language: verbal fluency, no. correct			0.38[c]	NS	--		
						Working memory: backward digit span, longest span recalled			0.12[c]	NS	--		
						Recall memory: word lists, total of 3 trials			-0.01[c]	NS	--		
						Mini-Mental State Examination			0.14[c]	NS	--		

Ref=reference group for comparisons

[a] Median intake
[b] All RRs were adjusting for age, smoking, total energy intake, alcohol consumption, caffeine intake, and lactose intake
[c] Final cognitive measures regressed onto baseline diet, adjusted for baseline cognitive measures, age, education, smoking, alcohol intake, BMI, diabetes (yes or no), systolic blood pressure, time of second measure relative to folic acid fortification, time interval between the 2 cognitive measures, and total energy intake. All outcomes and dietary intake measures were log-transformed.
[d] Slope for the multivariate linear regression model

Table 17. Association between dietary intake levels of folate and neurodegenerative diseases or cognitive function in longitudinal studies

Author Year Country	Baseline Population	Baseline Mean Age (yr)	N	Study Design (Follow-up Duration)	Dietary Assessment Method	Outcomes	Mean Daily Intake (µg/day)		Results: RR /OR, β[i]	Results: P_{btw} / (95%CI)	Results: P_{trend}	Applicability	Quality
Chen, 2004 US	Normal, all	30-75	136,057	Prospective nested case-control study (Mean 12.7 yr in men & 17.3 yr in women)	Food frequency questionnaire, validated	Risk of newly developed PD cases analyzed by Cox proportional hazard models	Quintile 1	nd	1.0[b]	Ref	NS	👪	A
							Quintile 2	nd	1.2	(0.9, 1.8)			
							Quintile 3	nd	1.4	(1.0, 2.0)			
							Quintile 4	nd	1.3	(0.9, 1.8)			
							Quintile 5	nd	1.2	(0.8, 1.7)			
	Normal, men	40-75	47,341				Quintile 1	244[a]	1.0[b]	Ref	NS		
							Quintile 2	317[a]	1.2	(0.8, 1.9)			
							Quintile 3	388[a]	1.4	(0.9, 2.1)			
							Quintile 4	517[a]	1.2	(0.8, 1.8)			
							Quintile 5	841[a]	1.1	(0.7, 1.7)			
	Normal, women	30-55	88,716				Quintile 1	158[a]	1.0[b]	Ref	NS		
							Quintile 2	217[a]	1.3	(0.7, 2.3)			
							Quintile 3	277[a]	1.6	(0.9, 2.7)			
							Quintile 4	393[a]	1.5	(0.9, 2.6)			
							Quintile 5	699[a]	1.4	(0.8, 2.4)			
Morris, 2005 US	Normal, all	74	3,718	Prospective longitudinal cohort study (median 5.5 yr)	Food frequency questionnaire, validated	Rates of cognitive change[j] per year analyzed by multivariate mixed effect model	Quintile 1	186[a]	--	Ref	<0.001	👪	A
							Quintile 2	251[a]	-0.01[h]	.41			
							Quintile 3	311[a]	-0.01[h]	.38			
							Quintile 4	419[a]	-0.02[h]	.04			
							Quintile 5	742[a]	-0.02[h]	.002			
							Quintile 1	175[g,a]	--	Ref	0.04		
							Quintile 2	227[g,v]	-0.01[h]	.04			
							Quintile 3	258[g,a]	-0.01[h]	.05			
							Quintile 4	312[g,a]	-0.01[h]	.06			
							Quintile 5	382[g,a]	-0.02[h]	.02			
							Supplement dose	0	--	Ref	nd		
								1-200	-0.01[h]	.25			
								201-399	-0.01[h]	.18			
								400	-0.01[h]	.22			
								401-1200	-0.03[h]	.001			

Continued

Table 17 Association between dietary intake levels of folate and neurodegenerative diseases or cognitive function in longitudinal studies (Continued)

Author Year Country	Baseline Population	Baseline Mean Age (yr)	N	Study Design (Follow-up Duration)	Dietary Assessment Method	Outcomes	Mean Daily Intake (µg/day)		Results: RR /OR, β[i]	Results: P_{btw} / *(95%CI)*	Results: P_{trend}	Applicability	Quality
Tucker, 2005	Normal, men	67	241-287	Prospective longitudinal cohort study (mean 3 years)	Food frequency questionnaire, validated	Constructional praxis: spatial copying, sum of drawings	440 ± 202 SD (range 80-1216) (N=321)		0.67[k]	<.0001	--	🚹🚹	B
						Language: verbal fluency, no. correct			1.44[k]	<.05	--		
						Working memory: backward digit span, longest span recalled			0.11[k]	NS	--		
						Recall memory: word lists, total of 3 trials			0.31[k]	NS	--		
						Mini-Mental State Examination			0.08[k]	NS	--		
						Change in figure copying score	Tertile 1	<339	-0.55[l]	Ref	<.01		
							Tertile 2	339-523	-0.25[m]	NS			
							Tertile 3	>523	+0.25[m]	<.01			
Mizrahi, 2003 US	AD[f]	74	<64[c]	Retrospective case-control study (3 age periods: 20-39, 40-59; 60+ yr old)	Food frequency questionnaire	Diagnosis of probable AD, fulfilling NINCDS/ADRDA criteria	20-39 yr	155[d]	nd	NS[e]	nd	🚹🚹🚹	C
							40-59 yr	170[d]		NS[e]			
							60+ yr	210[d]		.01[e]			
	Normal	75	<64[c]				20-39 yr	150[d]	nd	Ref	nd		
							40-59 yr	150[d]		Ref			
							60+ yr	155[d]		Ref			

Ref=reference group for comparisons

[a] Median intake
[b] All RRs were adjusting for age, smoking, total energy intake, alcohol consumption, caffeine intake, and lactose intake
[c] Missing data on dietary intake for some of the participants resulted in different sample sizes for the various time periods
[d] Values were estimated from graphs. Intake amount is per 1000 Kcal
[e] Two-sample t-tests were used to compare the mean levels of dietary folate or vitamin B6 for AD patients and controls (reference group) at 3 age periods separately. These analyses were not adjusted for any confounders
[f] The ZIG-scale consists of ZIG-A scale (cognitive functioning), ZIG-B scale (social functioning) and the ZIG-C scale (social functioning). The ranges of the ZIG-scales are from 6 to 24. The higher the point, the worse the outcome. For the purpose of this review, we only look at the results of ZIG-A scale.
[g] Folate from food intake only (or excluding intake from supplements)
[h] Multiple-adjusted model includes terms including age, quintiles of folate intake, time, total energy, sex, education, race, vitamin E intake from food, total vitamin C intake, and time interactions with all covariates. The model from folate intake from food sources also includes terms for multivitamin use (yes or no)
[i] Slope for the multivariate linear regression model
[j] Changes in the computed z scores for the 4 cognitive tests and averaged the scores for a global measure of cognitive function. The 4 cognitive tests included the East Boston Tests of immediate and delayed recall, the Mini-Mental State Examination, and the Symbol Digit Modalities Test of perceptual speed and attention.

[k] Final cognitive measures regressed onto baseline diet, adjusted for baseline cognitive measures, age, education, smoking, alcohol intake, BMI, diabetes (yes or no), systolic blood pressure, time of second measure relative to folic acid fortification, time interval between the 2 cognitive measures, and total energy intake. All outcomes and dietary intake measures were log-transformed.
[l] Mean change in score from baseline
[m] Estimated value from graphs

Cross-Sectional Studies

Study Descriptions. Five cross-sectional studies examined the association between the dietary intake levels of B vitamins and cognitive function or the risk of age-related neurodegenerative disease.[65,92-95] Of the five studies, three were of fair quality and two were of poor quality.

Overall Effects

Thiamine (B1). Three studies associated participants' dietary intake levels of thiamine to their cognitive function scores.[92,93,95] One additional study compared the dietary intake levels of thiamine in participants with AD to that in normal participants (Table 18).[94] No statistically significant association was found between the dietary intake levels of thiamine and cognitive function scores, except for Goodwin 1983 that found that participants who were in bottom 5 percent of thiamine intake levels had significantly worse Wechsler verbal memory test scores than those who were in the top 90 percent. Renvall 1989 found that participants with AD had similar dietary intake levels of thiamine as normal participants.

Riboflavin (B2). The same four studies that evaluated thiamine also assessed participants' dietary intake levels of vitamin B2 (Table 19).[92-95] Similar results were found except that Goodwin 1983 found that participants who were in bottom 10 percent of vitamin B2 intake levels had significantly worse Wechsler verbal memory test scores than those who were in the top 90 percent. In addition, Lee 2001 found that, adjusting for age, the dietary intake levels of vitamin B2 increased with MMSE scores among women, but not among men.

Pyridoxine (B6). Three studies associated participants' dietary intake levels of vitamin B6 with cognitive function scores (Table 20).[65,92,95] No statistically significant association was found between the dietary intake levels of vitamin B6 and cognitive function scores, except for Goodwin 1983, which found that participants who were in bottom 10 percent, but not the bottom 5 percent, of B6 intake levels had significantly worse Wechsler verbal memory test scores than those who were in the top 90 percent.

Cyanocobalamin (B12). Three studies associated participants' dietary intake levels of vitamin B12 to their cognitive function scores (Table 21).[65,92,95] One additional study compared the dietary intake levels of vitamin B12 in participants with AD to that in normal participants.[94] No statistically significant association was found between the dietary intake levels of vitamin B12 and cognitive function scores or AD.

Folate. The same four studies that evaluated vitamin B12 intake also tested folate intake (Table 22)[65,92,94,95] No statistically significant association was found between the dietary intake levels of folate and cognitive function scores, except for Goodwin 1983 that found that participants who were in bottom 5 percent of folate intake levels had significantly worse Wechsler verbal memory

test scores than those who were in the top 90 percent. Renvall 1989 found that participants with AD had similar dietary intake levels of folate as normal participants.

Summary. Among the five studies, only two found any significant associations between vitamin B intake and cognitive function scores. One study found that subjects with low intake of vitamins B1, B2, B6, and folate, but not vitamin B12, scored significantly worse on verbal memory than those with relatively high intake levels. One study also found association between vitamin B2 intake and MMSE score in women, but not in men. No association between dietary intake of B12 and cognitive function or diagnosis of AD was found in all five studies.

Table 18. Association between dietary intake of vitamin B1 (thiamine) and cognitive function in cross-sectional studies

Author Year Country	Population	Mean Age (yr)	N	Dietary Assessment Method	Subgroups	Mean Cognitive Score, Cognitive Score Used, or Cut-off	Vitamin B1 Intake (mg/day) Mean±SD	Results				Applicability	Quality
								n	r	Effect	P		
Goodwin, 1983 US	Normal	72	260	3-day food records, weighing food	All subjects	Wechsler verbal memory test (WMT) ⭱	nd	260	-0.02	↔	NS[g]	🚻	B
					Mean intake ≤5%	WMT score ⭱ = ~4.8[f]	nd	nd		↑	<.05[h]		
					Mean intake ≤10%	WMT score ⭱ = ~5.3[f]	nd	nd		↔	NS[h]		
					Mean intake >90%	WMT score ⭱ = ~6.2[f]	nd	nd		Ref			
Requejo, 2003 Spain	Normal	≥65	168	5-day food records, weighting food	Age<75th %tile	MMSE ⭱ ≥ 28[a]	1.12 ± 0.34	nd		~↑	<.1	🚻	B
						MMSE ⭱ < 28	1.05 ± 0.29	nd					
					Age≥75th %tile	MMSE≥28	1.12 ± 0.44	nd		~↑	<.1		
						MMSE< 28	0.96 ± 0.23	nd					
Lee, 2001 Korea	Normal, men	72	210	Single 24-hr dietary recall	Normal	MMSE-K ⭱ ≥ 24	0.95 ± 0.35	136				🚻	C
					Inadequate	MMSE-K ⭱ 19-24	0.91 ± 0.34	48	0.083[c]	↔	NS		
					Poor	MMSE-K ⭱ ≤ 19	0.82 ± 0.27	26					
	Normal, women	70	239		Normal	MMSE-K ⭱ ≥ 24	0.91 ± 0.39	86					
					Inadequate	MMSE-K ⭱ 19-24	0.90 ± 0.63	79	0.13[c]	↔	NS		
					Poor	MMSE-K ⭱ ≤ 19	0.71[e] ± 0.35	74					
Renvall, 1989 US	SDAT[d]	77	<22[b]	3-day food records	SDAT	nd	1.40 ± 0.50	15		↔	NS	🚻	C
	Normal	71	<41[b]		Normal	nd	1.20 ± 0.40	33					

⭱ Higher score indicates better cognitive function. ⭳ Lower score indicates better cognitive function. %tile=percentile; SDAT=senile dementia of the Alzheimer's type; Ref=reference group for the comparisons; MMSE-K= Mini-Mental State Examination for Koreans

↑ Increase of the intake level correlate with a better outcome, or decrease of the intake level correlate with a worse outcome

↔ No association between the intake level and the outcome

↓ Increase of the intake level correlate with a worse outcome

[a] Folstein's MMSE was used. Points are awarded between 0 and 35, with 28 or more considered as normal.

[b] Only subjects who had both dietary and biochemical data were analyzed.

[c] Controlling for age

[d] Free living subjects

[e] Mean was significantly lower (Duncan's multiple range test, $P<0.05$) than other groups.

[f] Values were estimated from graphs

[g] The study also performed a multivariate analysis controlling for age and sex of the subject and the correlation remained not significant.

[h] Adjusted for unequal variances

Table 19. Association between dietary intake of vitamin B2 (riboflavin) and cognitive function in cross-sectional studies

Author Year Country	Population	Mean Age (yr)	N	Dietary Assessment Method	Subgroups	Mean Cognitive Score, Cognitive Score Used, or Cut-off	Vitamin B2 Intake (mg/day) Mean±SD	Results				Applicability	Quality
								n	r	Effect	P		
Goodwin, 1983 US	Normal	72	260	3-day food records, weighing food	All subjects	Wechsler verbal memory test (WMT) ⇑	nd	260	0.02	↔	NS[g]	👥	B
					Mean intake ≤5%	WMT score ⇑ = ~4.5[f]	nd	nd		↑	<.05[h]		
					Mean intake ≤10%	WMT score ⇑ = ~4.25[f]	nd	nd		↑	<.01[h]		
					Mean intake >90%	WMT score ⇑ = ~6.3[f]	nd	nd		Ref			
Requejo, 2003 Spain	Normal	≥65	168	5-day food records, weighting food	Age<75th %tile	MMSE ⇑ ≥ 28[a]	1.43 ± 0.40	nd		↔		👥	B
						MMSE ⇑ < 28	1.39 ± 0.35	nd					
					Age≥75th %tile	MMSE ⇑ ≥ 28	1.52 ± 0.43	nd		↔			
						MMSE ⇑ < 28	1.46 ± 0.38	nd					
Lee, 2001 Korea	Normal, men	72	210	Single 24-hr dietary recall	Normal	MMSE-K ⇑ ≥ 24	0.87 ± 0.46	136				👥	C
					Inadequate	MMSE-K ⇑ 19-24	0.77 ± 0.37	48	+0.08[c]	↔			
					Poor	MMSE-K ⇑ ≤ 19	0.74 ± 0.32	26					
	Normal, women	70	239		Normal	MMSE-K ⇑ ≥ 24	0.68 ± 0.33	86					
					Inadequate	MMSE-K ⇑ 19-24	0.72 ± 0.50	79	+0.11[c]	↑	<.05		
					Poor	MMSE-K ⇑ ≤ 19	0.50[e] ± 0.32	74					
Renvall, 1989 US	SDAT[d]	77	<22[b]	3-day food records	SDAT	nd	1.60 ± 0.60	14				👥	C
	Normal	71	<41[b]		Normal	nd	1.50 ± 0.60	37		↔			

⇑ Higher score indicates better cognitive function. ⇓ Lower score indicates better cognitive function. %tile=percentile; Ref=reference group for the comparisons; SDAT=senile dementia of the Alzheimer's type; MMSE-K= Mini-Mental State Examination for Koreans

↑ Increase of the intake level correlate with a better outcome, or decrease of the intake level correlate with a worse outcome

↔ No association between the intake level and the outcome

↓ Increase of the intake level correlate with a worse outcome

[a] Folstein's MMSE was used. Points are awarded between 0 and 35, with 28 or more considered as normal.

[b] Only subjects who had both dietary and biochemical data were analyzed.

[c] Controlling for age

[d] Free living subjects

[e] Mean was significantly lower (Duncan's multiple range test, p<0.05) than other groups.

[f] Values were estimated from graphs

[g] The study also performed a multivariate analysis controlling for age and sex of the subject and the correlation remained not significant.

[h] Adjusted for unequal variances

Table 20. Association between dietary intake of vitamin B6 (pyridoxine) and cognitive function in cross-sectional studies

Author Year Country	Population	Mean Age (yr)	N	Dietary Assessment Method	Subgroups	Mean Cognitive Score, Cognitive Score Used, or Cut-off	Vitamin B6 Intake (mg/day) Mean±SD	Results				Applicability	Quality
								n	r	Effect	P		
Goodwin, 1983 US	Normal	72	260	3-day food records, weighing food	All subjects	Wechsler verbal memory test (WMT) ⇑	nd	260	-0.02	↔	NS[g]	🚻	B
					Mean intake ≤5%	WMT score ⇑ = ~5.5[f]	nd	nd		↔	NS[h]		
					Mean intake ≤10%	WMT score ⇑ = ~4.8[f]	nd	nd		↑	<.05[h]		
					Mean intake >90%	WMT score ⇑ = ~6.2[f]	nd	nd		Ref			
Requejo, 2003 Spain	Normal	≥65	168	5-day food records, weighting food	Age<75th %tile	MMSE ⇑ ≥ 28[a]	1.40 ± 0.39	nd		↔	NS	🚻	B
						MMSE ⇑ < 28	1.39 ± 0.32	nd					
					Age≥75th %tile	MMSE ⇑ ≥ 28	1.36 ±0.48	nd		↔	NS		
						MMSE ⇑ < 28	1.40 ±0.31	nd					
Bryan, 2002 Australia	Normal	74	75	Food frequency questionnaire, validated	Intake in 1st quartile	Digit Symbol-Coding, Digit Span-Backwards, Digit-Symbol-Coding, and Vocabulary from Wechsler Adult Intelligence Scale-III; Stroop Test; Verbal Fluency; Initial Letter Fluency ⇑	1.20 ± 0.20	nd		↔	NS	🚹	B
					Intake in 2nd quartile		1.60 ±0.10	nd					
					Intake in 3rd quartile		2.10 ±0.10	nd					
					Intake in 4th quartile		2.80 ±0.40	nd					

⇑ Higher score indicates better cognitive function. ⇓ Lower score indicates better cognitive function. %tile=percentile; Ref=reference group for the comparisons
↑ Increase of the intake level correlate with a better outcome, or decrease of the intake level correlate with a worse outcome
↔ No association between the intake level and the outcome
↓ Increase of the intake level correlate with a worse outcome

[a] Folstein's MMSE was used. Points are awarded between 0 and 35, with 28 or more considered as normal.
[f] Values were estimated from graphs
[g] The study also performed a multivariate analysis controlling for age and sex of the subject and the correlation remained not significant.
[h] Adjusted for unequal variances

Table 21. Association between dietary intake of vitamin B12 and cognitive function in cross-sectional studies

Author Year Country	Population	Mean Age (yr)	N	Dietary Assessment Method	Subgroups	Mean Cognitive Score, Cognitive Score Used, or Cut-off	Vitamin B12 Intake (µg/day) Mean±SD	Results				Applicability	Quality
								n	r	Effect	P		
Goodwin, 1983 US	Normal	72	260	3-day food records, weighing food	All subjects	Wechsler verbal memory test (WMT) ⇑	nd	260	0.07	↔	NS[g]	👫	B
					Mean intake ≤5%	WMT score ⇑ = ~5.8[f]	nd	nd		↔	NS[h]		
					Mean intake ≤10%	WMT score ⇑ = ~5.9[f]	nd	nd		↔	NS[h]		
					Mean intake >90%	WMT score ⇑ = ~6.1[f]	nd	nd		Ref			
Requejo, 2003 Spain	Normal	≥65	168	5-day food records, weighting food	Age<75th %tile	MMSE ⇑ ≥ 28[a]	7.3 ± 7.9	nd		↔	NS	👫	B
						MMSE ⇑ < 28	5.9 ± 5.6	nd					
					Age≥75th %tile	MMSE ⇑ ≥ 28	7.3 ± 5.4	nd		↔	NS		
						MMSE ⇑ < 28	7.4 ± 8.0	nd					
Bryan, 2002 Australia	Normal	74	75	Food frequency questionnaire, validated	Intake in 1st quartile	Digit Symbol-Coding, Digit Span-Backwards, Digit-Symbol-Coding, and Vocabulary from Wechsler Adult Intelligence Scale-III; Stroop Test; Verbal Fluency; Initial Letter Fluency ⇑	2.1 ±0.6	nd		↔	NS	🧍	B
					Intake in 2nd quartile		3.3 ± 0.3	nd					
					Intake in 3rd quartile		4.2 ± 0.4	nd					
					Intake in 4th quartile		8.4 ± 5.2	nd					
Renvall, 1989 US	SDAT[d]	77	<22[b]	3-day food records	SDAT	nd	2.3 ± 1.8	21		↔	NS	👫	C
	Normal	71	<41[b]		Normal	nd	2.9 ± 2.3	22					

⇑ Higher score indicates better cognitive function. ⇓ Lower score indicates better cognitive function. %tile=percentile; Ref=reference group for the comparisons
↑ Increase of the intake level correlate with a better outcome, or decrease of the intake level correlate with a worse outcome
↔ No association between the intake level and the outcome
↓ Increase of the intake level correlate with a worse outcome

[a] Folstein's MMSE was used. Points are awarded between 0 and 35, with 28 or more considered as normal.
[b] Only subjects who had both dietary and biochemical data were analyzed.
[d] Free living subjects
[f] Values were estimated from graphs
[g] The study also performed a multivariate analysis controlling for age and sex of the subject and the correlation remained not significant.
[h] Adjusted for unequal variances

Table 22. Association between dietary intake of folate and cognitive function in cross-sectional studies

Author Year Country	Population	Mean Age (yr)	N	Dietary Assessment Method	Subgroups	Mean Cognitive Score, Cognitive Score Used, or Cut-off	Folate Intake (µg/day) Mean±SD	Results n	Results r	Results Effect	Results P	Applicability	Quality
Goodwin, 1983 US	Normal	72	260	3-day food records, weighing food	All subjects	Wechsler verbal memory test (WMT) ⇑	nd	260	-0.06	↔	NS[g]	🚻	B
					Mean intake ≤5%	WMT score ⇑ = ~4.5[f]	nd	nd		↑	<.05[h]		
					Mean intake ≤10%	WMT score ⇑ = ~5.4[f]	nd	nd		↔	NS[h]		
					Mean intake >90%	WMT score ⇑ = ~6.15[f]	nd	nd		Ref			
Requejo, 2003 Spain	Normal	≥65	168	5-day food records, weighting food	Age<75th %tile	MMSE ⇑ ≥ 28[a]	202 ± 74	nd		↔	NS	🚻	B
						MMSE ⇑ < 28	183 ± 61	nd					
					Age≥75th %tile	MMSE ⇑ ≥ 28	223 ± 114	nd		↔	NS		
						MMSE ⇑ < 28	181 ± 64	nd					
Bryan, 2002 Australia	Normal	74	75	Food frequency questionnaire, validated	Intake in 1st quartile	Digit Symbol-Coding, Digit Span-Backwards, Digit-Symbol-Coding, and Vocabulary from Wechsler Adult Intelligence Scale-III; Stroop Test; Verbal Fluency; Initial Letter Fluency ⇑	203 ± 26	nd		↔	NS	🚹	B
					Intake in 2nd quartile		266 ± 13	nd					
					Intake in 3rd quartile		326 ± 19	nd					
					Intake in 4th quartile		467 ± 79	nd					
Renvall, 1989 US	SDAT[d]	77	<22[b]	3-day food records	SDAT	nd	169 ±74	27?		↔	NS	🚻	C
	Normal	71	<41[b]		Normal	nd	186 ± 71	10					

⇑ Higher score indicates better cognitive function. ⇓ Lower score indicates better cognitive function. %tile=percentile; Ref=reference group for the comparisons; ?=value doesn't make sense perhaps due to reporting error

↑ Increase of the intake level correlate with a better outcome, or decrease of the intake level correlate with a worse outcome

↔ No association between the intake level and the outcome

↓ Increase of the intake level correlate with a worse outcome

[a] Folstein's MMSE was used. Points are awarded between 0 and 35, with 28 or more considered as normal.

[b] Only subjects who had both dietary and biochemical data were analyzed.

[d] Free living subjects

[f] Values were estimated from graphs

[g] The study also performed a multivariate analysis controlling for age and sex of the subject and the correlation remained not significant.

[h] Adjusted for unequal variances

Association of Tissue Levels of B Vitamins to Age-Related Neurodegenerative Diseases

Thiamine (Vitamin B1) Level Association Studies

Study Descriptions. Eight cross-sectional studies examined the association of thiamine levels with diagnosis or cognitive function.[99-106] Four of these studies measured serum, plasma, and RBC levels of thiamine among AD, non-AD, PD, and cognitively impaired subjects (Table 23). Four other studies reported the plasma, cerebrospinal fluid (CSF), and brain levels of thiamine diphosphate (TDP), the active form of thiamine in the brain (Table 24). The sample size for the cross-sectional studies ranged from 34 to 290. The two studies by Mastrogiacoma 1996 and Molina 2002, which reported brain or CSF levels of thiamine derivatives (free thiamine, total thiamine, thiamine monophosphate, thiamine diphosphate), compared the levels between AD and normal controls. Jimenez-Jimenez 1999 compared the CSF levels of thiamine derivatives between PD and controls. Snowdon 2000 compared the thiamine levels from stored blood within a subset of AD subjects who had histologically significant and non-significant lesions in the brain at autopsy. All studies were graded moderate to poor quality (3 B, 5 C). Three studies have broad applicability, two moderate, and three narrow applicability.

Overall Effect. Four studies evaluated plasma and/or RBC thiamine or thiamine pyrophosphate (TPP), two of which found significantly greater deficiency among AD subjects compared to PD or controls (Table 23). Four other studies evaluated thiamine or thiamine derivatives in CSF, plasma, and cerebral cortex (Table 24). Two of these reported significantly reduced levels of thiamine derivatives in plasma or cerebral cortex among AD subjects and one among subjects with PD.

Gold 1995 examined the thiamine levels in the plasma and RBCs and found significantly low plasma thiamine levels and a high prevalence of plasma thiamine deficiency, but not for RBC thiamine, among probable AD, compared to non-AD subjects. A subsequent publication by the same author (Gold 1998) evaluated thiamine levels in the plasma and RBC thiamine among AD and PD subjects, and reported similar significantly lower levels and higher prevalence of plasma thiamine among AD subjects. The plasma level of thiamine among PD subjects was normal. Assantachai 1997 estimated serum levels and reported a high, but non-significant prevalence of thiamine deficiency among cognitively impaired compared to normal elderly subjects. Scillepi 1984 reported normal mean thiamine levels among AD and non-AD subjects.

Jimenez-Jimenez 1999 compared CSF levels of thiamine and its phosphate esters among PD patients and normal controls. All thiamine derivatives in the CSF except free thiamine were normal among PD patients. Molina 2002 compared subjects with AD to normal controls. This study examined CSF and plasma levels of thiamine derivatives and reported significantly lower plasma levels of thiamine derivatives among AD subjects. Among a subset of AD patients annual mean decreases in MMSE score was assessed and there were no significant differences in mean MMSE scores with high versus low thiamine levels. Mastrogiacoma 1996 examined thiamine derivatives in autopsied cerebral cortex among AD and normal subjects. The mean levels of TDP in the temporal, parietal, occipital areas of cerebral cortex were slightly, but significantly reduced by 18 to 21 percent among AD subjects compared to normal subjects. The levels of other thiamine derivatives were normal among AD subjects. Snowdon 2000 described a negative, but non-significant correlation of serum thiamine levels with severity of cerebral cortex

atrophy among AD subjects with histologically significant lesions. AD subjects with histologically non-significant lesions had a positive, but non-significant correlation of serum thiamine levels with severity of atrophy of the cerebral cortex.

Interactions and Covariates. Gold 1998 (Table 23) performed secondary analyses excluding four PD patients less than 60 years of age, matching the two groups for age. They found significant differences in both the plasma thiamine levels and the prevalence of thiamine deficiency (defined as plasma or RBC thiamine values below the range of normal for their respective age group) between AD, and PD subjects. Snowdon 2000 (Table 24) adjusted age as a potential confounder in the correlation analyses, but other studies did not adjust for potential confounders. No longitudinal studies evaluated the association of thiamine and cognitive function.

Summary. Overall, eight cross-sectional studies evaluated levels of thiamine among AD, cognitively impaired and PD patients. Three studies reported significantly reduced mean thiamine or TDP levels in the plasma and brain among AD subjects, and one reported similar reduction in mean levels of thiamine derivative among PD subjects. None of the studies that showed significant results adjusted for potential confounders. The remaining four studies found no differences between the investigated groups.

Table 23. Association of thiamine (vitamin B1) levels and prevalence of thiamine deficiency with cognitive function

Author Year	Population	Mean Age (yr)	N	Thiamine Level (ng/mL)					Thiamine deficient		Applicability	Quality
				Tissue	Mean	SD	Normal Range	*P* [a]	%	*P* [b]		
Assantachai 1997	Cognitive impaired	69	63	Blood	12.4	8.8	0-15% [c]	NS	30.2	NS	🧍🧍🧍	B
	Normal	69	138		10.9	7.7						
Gold 1998	AD	78	17	Plasma	7.5	4.1	11-12 [d]	<.001	65	<.001	🧍	B
	PD	71	33		11.1	4.1			11			
	AD	78	17	RBC	149.9	34.6	140-146 [e]	NS	nd			
	PD	71	33		146.8	43.1						
Scileppi 1984	AD	nd	55	Plasma	46	4	>25	NS	nd		🧍🧍	C
	Non-AD	nd	58		48	4						
Gold 1995	AD	78	17	Plasma	7.5	4.1	11-12 [d]	.002	65	<.001	🧍🧍	C
	Non-AD	75	17		12.6	5.4			12			
	AD	78	17	RBC	149.9	34.6	140-146 [e]	.07	18	NS		
	Non-AD	75	17		168.0	47.8			0			

SD: standard deviation; NS: non-significant

[a] *P* values for comparing mean levels of thiamine.
[b] *P* values for comparing percent with thiamine deficiency.
[c] Blood level of thiamine pyrophosphate (TPP).
[d] Plasma: Normal mean (range): Age 61-80: 12.0 (8-26); Age 81+: 11.0 (10-12.6) ng/mL.
[e] RBC: Normal mean (range): Age 61-80: 146.0 (89-205); Age 81+: 140.0 (131-163) ng/mL.

Table 24. Association of levels of thiamine or thiamine derivatives (vitamin B1) with diagnoses of age related neurocognitive disorders

Author Year	Population	Mean Age (yr)	N	Thiamine or thiamine derivative description	B Vitamin Level					Applicability	Quality
					Tissue (units)	Mean	SD	Correlation or % of Change [a]	*P*		
Snowdon 2000	AD with lesions [b]	91	15	B1 level correlating with atrophy	Serum nmol/L	142	36	r=-0.49	NS	🧍	B
	AD without lesions [c]	91	15			148	30	r=+0.05	NS		
Molina 2002	AD	73	33	Total thiamine	CSF nmol/L	7.29	6.98		NS	🧍🧍🧍	C
	Normal	70	32			9.46	4.52				
	AD	73	33	Free thiamine		1.17	3.03		NS		
	Normal	70	32			2.20	3.20				
	AD	73	33	TMP		3.57	3.84		NS		
	Normal	70	32			4.30	2.40				
	AD	73	33	TDP		2.55	1.70		NS		
	Normal	70	32			3.21	2.28				
Molina 2002	AD	73	33	Total thiamine	Plasma nmol/L	4.75	7.72		<.05	🧍🧍🧍	C
	Normal	70	32			7.88	5.79				
	AD	73	33	Free thiamine		1.16	1.21		<.05		
	Normal	70	32			2.61	2.93				
	AD	73	33	TMP		1.32	2.02		NS		
	Normal	70	32			2.20	3.20				
	AD	73	33	TDP		2.22	1.74		<.05		
	Normal	70	32			3.23	1.87				
Jimenez-Jimenez 1999	PD	64	24	Total thiamine	CSF nmol/L	9.1	6.4		NS	🧍🧍🧍	C
	Normal	63	40			9.3	5.1				
	PD	64	24	Free thiamine		0.9	1.3		<.01		
	Normal	63	40			1.9	1.4				
	PD	64	24	TDP		3.9	3.0		NS		
	Normal	63	40			3.1	2.3				
	PD	64	24	TMP		4.3	3.3		NS		
	Normal	63	40			4.3	2.9				

Continued

Table 24. Association of levels of thiamine or thiamine derivatives (vitamin B1) with diagnoses of age related neurocognitive disorders (Continued)

Author Year	Population	Mean Age (yr)	N	Thiamine or thiamine derivative description	B Vitamin Level					Applicability	Quality
					Tissue (units)	Mean	SD	Correlation or % of Change [a]	*P*		
Mastrogiacoma 1996	AD	73	20	Total thiamine	Temporal cortex pmol/mg	27.2	1.4	-11%	NS	↟	C
	Normal	70	18			30.7	1.3				
	AD	73	20	Thiamine		9.0	0.7	-1%	NS		
	Normal	70	18			9.0	0.7				
	AD	73	20	TMP		3.4	0.3	+13%	NS		
	Normal	70	18			3.0	0.4				
	AD	73	20	TDP		14.8	0.8	-20%	<.01		
	Normal	70	18			18.6	0.9				
Mastrogiacoma 1996	AD	73	20	Total thiamine	Parietal cortex pmol/mg	29.5	1.4	-5%	NS	↟	C
	Normal	70	18			31.1	1.3				
	AD	73	20	Thiamine		9.9	0.8	+9%	NS		
	Normal	70	18			9.1	0.6				
	AD	73	20	TMP		3.9	0.4	+26%	NS		
	Normal	70	18			3.1	0.3				
	AD	73	20	TDP		15.7	0.7	-18%	<.01		
	Normal	70	18			19.1	1.0				
Mastrogiacoma 1996	AD	73	20	Total thiamine	Occipital cortex pmol/mg	27.9	1.4	-12%	NS	↟	C
	Normal	70	18			31.6	1.3				
	AD	73	20	Thiamine		10.1	0.8	-8%	NS		
	Normal	70	18			11.0	0.7				
	AD	73	20	TMP		3.7	0.4	+12%	NS		
	Normal	70	18			3.3	0.3				
	AD	73	20	TDP		14.1	0.6	-21%	<.01		
	Normal	70	18			17.8	1.0				

NS: non-significant; TDP: thiamine diphosphate; TMP: thiamine monophosphate; SD: standard deviation

[a] Percent of change: mean levels of thiamine derivative in the AD compared to controls.
[b] AD with histologically significant lesions at autopsy.
[c] AD without histologically significant lesions at autopsy.

Riboflavin (Vitamin B2) Level Association Studies

Study Descriptions. Two studies [106,107] reported cross-sectional data on riboflavin (B2) levels among AD, PD, and dementia subjects. One study compared blood levels of B2 in AD with control subjects, and the other compared plasma levels of B2 in PD with dementia subjects. Scileppi 1984 assessed blood levels of 12 vitamins among 55 AD subjects. The control group included a total of 58 normal, depressed, vascular and mixed dementia subjects. Coimbra 2003 assessed plasma levels of B2 among 31 PD subjects compared with 10 dementia subjects without stroke. These studies were assessed to be of poor quality (C) and moderate applicability.

Overall Effect. Scileppi 1984 reported no significant differences in the riboflavin levels between AD and the control groups. Coimbra 2003 found a mean plasma B2 level below normal among PD subjects, which was significantly lower than among subjects with dementia. Neither study adjusted for any confounders.

Summary. Two poor quality studies assessed the cross-sectional levels of riboflavin among AD, PD, dementia, and other control groups. One study reported no significant difference between AD and control subjects. The second reported lower plasma levels among PD subjects with a significant difference between PD and dementia subjects.

Table 25. Association of riboflavin (vitamin B2) levels with diagnosis of neurocognitive disorders

Author Year	Population	Mean Age (yr)	N	Plasma Riboflavin Level (ng/mL)				Applicability	Quality
				Mean	SD	Normal Range	*P*		
Scileppi 1984	AD	nd	55	295	10	>110	NS	🚻	C
	Non-AD		58	292	9				
Coimbra 2003	PD	68	31	100.9	22.0	125-300	<.01	🚻	C
	Dementia w/o Stroke	78	10	128.8	25.6				

SD: standard deviation; NS: non-significant

Vitamin B6 Level Association Studies

Study Descriptions. Ten studies examined the association of vitamin B6 serum levels with the diagnosis of dementia or cognitive impairment, and cognitive function, including three prospective longitudinal studies, one case control study, one retrospective cohort study, and five cross-sectional studies.[18,105-111] Pyridoxal-5'-phosphate (PLP), an active coenzyme form of B6, was used to estimate B6 serum levels in all but two studies; one did not report the method for estimating B6[111] and another study used a protozoological assay.[105] The longitudinal studies recruited 313 to 1,092 participants, the case control study 80 subjects while the sample size for the other studies ranged from 30 to 127. Studies had narrow to broad applicability. Two of the longitudinal studies, the case control study and the retrospective cohort were of moderate quality (B) while the third longitudinal study and the five cross-sectional studies were of low quality (C).

One longitudinal study recruited participants with normal cognitive function and investigated whether low baseline levels for vitamin B6 may be a risk factor for cognitive decline after about 3 years of follow-up (Table 26).[112] Cognitive decline was defined as 7 year cognitive change with at least a 9-point drop of the total cognitive score (the sum of all subtest scores). Another longitudinal study also recruited participants with normal cognitive function and tried to

correlate cognitive function after almost 8 years of follow-up with the baseline levels of vitamin B6 (Table 26).[96] Cognitive function in this study was assessed by MMSE score, as well as by tests on construction praxis, language, working and recall memory. In the third longitudinal study, subjects with normal cognitive function were followed for a median of 8 years and new cases of AD or dementia were recorded (Table 26).[18] The case control study compared the number of subjects with low PLP among patients with AD with that among individuals with intact cognitive function.[109] The retrospective cohort study correlated the number of lesions in autopsies of women with AD with B6 levels[105] while the rest of cross-sectional studies compared the mean B6 serum levels between different groups of participants, one comparing patients with AD, persons cognitively impaired but not demented, and normal participants; another study compared patients with AD and patients with other dementias; another comparing patients with AD and normal individuals; and the other two comparing patients with PD to patients with dementia, or to normal subjects (Table 27).

Overall Effect. Seshadri 2002, in the longitudinal study, reported that B6 serum levels were not correlated with the risk of AD or other dementias after adjusting for age, sex, and ApoE genotype; although specific results were not provided. Kado 2005 did not find any significant increase in the risk for cognitive decline for participants with very low vitamin B6 levels after adjusting for age, sex, education, baseline cognitive function, baseline physical function, and smoking. However, Tucker 2005, after adjusting for baseline cognitive measures, age, education, smoking, alcohol intake, BMI, diabetes, systolic blood pressure, time of second measure relative to folic acid fortification, time interval between the two cognitive measures, and serum creatinine, reported a significant correlation between higher levels of vitamin B6 at baseline and better performance in the figure copying test after 3 years of follow-up (β=0.38, P <0.05). No other significant association was described in the same study between vitamin B6 levels and the score of other cognitive tests.

None of the cross-sectional studies found any significant correlation between B6 levels and diagnosis of AD or number of AD lesions in brain autopsy, cognitive impairment, or dementia. In addition, two cross-sectional studies found no association between B6 level and diagnosis of PD, compared to either people with dementia or normal people.

Interactions and Covariates. Generally, results were non-significant irrespective of the study design. Woitalla 2004 examined the association of B6 levels and diagnosis of PD in patients with different MTHFR genotypes (CC, CT, TT). No significant difference was reported when the three genotype groups were compared to each other or to the non-PD participants. There was no evidence across studies of differences in association with tests of different cognitive domains.

Summary. Three prospective longitudinal studies, one case control study, one retrospective cohort, and five cross-sectional studies examined the potential correlation of B6 serum levels with the diagnosis of dementia or cognitive impairment, and cognitive function. The studies were generally of low quality and had narrow to broad applicability. Only one of the longitudinal studies described a significant correlation between higher levels of vitamin B6 at baseline and better performance in the figure copying test after 3 years of follow-up. However, a similar association was not found for other cognitive tests that were assessed in the same study. It is uncertain whether the improvement in performance in the figure copying test is clinically important. Additionally, no statistically significant correlations were reported between B6 levels

and AD or number of AD lesions in brain autopsy, cognitive impairment, PD, or dementia. There is very limited, low quality evidence to allow conclusion for any association between B6 levels and prevention or regression of cognitive function decline.

Table 26. Association of serum PLP level with diagnosis of AD, dementia, cognitive decline and cognitive function status in longitudinal studies

Author Year	Baseline Population	Mean Age (yr)	N	Follow-up	B Vitamin Level (ng/mL) Mean	SD	Normal Range	Outcomes	Results		Applicability	Quality
Kado, 2005	Normal	74	370	7 yr	<8.7 ≥8.7		nd	Increased risk of cognitive decline [a]	RR 1.2 (95%CI 0.7-1.8) [b]		🧍🧍	B
Tucker, 2005	Normal	67	313 [c]	Mean 1092 days	21.3	20.8	≥4.9	MMSE ↑	β 0.15 [d]	NS	🧍🧍	B
								Construction praxis: spatial copying, sum of drawings ↑	β 0.38 [e]	*P*<.05		
								Language: verbal fluency ↑	β 0.56 [d]	NS		
								Working memory: backward digit span, longest span recalled ↑	β -0.03 [d]	NS		
								Recall memory: word lists, total of 3 trials ↑	β 0.33 [d]	NS		
Seshadri, 2002	Normal	76	1092 [f]	Median 8 yr (Range 1-13)	nd		Coefficient of variation 16%	Newly diagnosed AD; newly diagnosed dementia	After adjusting for age, sex, and ApoE genotype, B6 levels were not related to the risk of dementia or AD		🧍🧍🧍	C

↑ Higher score indicates better cognitive function. ↓ Lower score indicates better cognitive function. PLP, pyridoxal-5'-phosphate (active coenzyme form of B6); RR, Risk ratio; CI, confidence interval

[a] Defined as 7 year cognitive change ≥ 9-point drop (worst quartile).
[b] Adjusted for age, sex, education, baseline cognitive function, baseline physical function, and smoking; results non significant.
[c] For MMSE, N=271-275; for construction praxis, N=280-284; for language, N=239-243; for working memory, N=236-240; and for recall memory, N=235-239.
[d] β adjusted for baseline cognitive measures, age, education, smoking, alcohol intake, BMI, diabetes, systolic blood pressure, time of second measure relative to folic acid fortification, time interval between the two cognitive measures, and serum creatinine.
[e] β adjusted for baseline cognitive measures, age, education, smoking, alcohol intake, BMI, diabetes, systolic blood pressure, time of second measure relative to folic acid fortification, time interval between the two cognitive measures, and serum creatinine; figure copying score in participants with PLP<11.4 ng/mL decreased significantly compared to figure copying score in participants with PLP>21 ng/mL (-0.6 vs. +0.2, p<0.01).
[f] Of the total population N=1092, 92% had measurements for B6; not reported how many of these patients with B6 measurements developed dementia and/ or AD.

Table 27. Association of serum PLP level with diagnosis of AD, cognitive impairment, dementia, and PD in retrospective cohorts, case-control, and cross-sectional studies

Author Year	Population	Mean Age (yr)	N	B Vitamin Level (ng/mL)					Applicability	Quality
				Mean	SD	Normal Range	Correlation estimate	*P*		
Miller, 2002	AD	78	32	29.9	62.8		nd	NS [a]	🧍🧍	B
	AD with VD	82	11	18.3	14.6					
	Normal	75	22	15.8	9.1					
	Normal with VD	76	15	26.4	30.1					
Snowdon, 2000 [b]	With significant number of AD lesions (postmortem autopsy)	91	15	78.8	46.7		r = –0.38	NS	🧍	B
	Without significant number of AD lesions (postmortem autopsy)		15	71.7	16.1		r = +0.03	NS		
Kado, 2005	Participants in the bottom quartile of total cognitive score	74	499	<8.7	nd	nd	RR 1.37 (95%CI 0.96-?) [c]	NS [d]	🧍🧍	B
	Participants not in the bottom quartile of total cognitive score			≥8.7	nd					
Ravaglia, 2000 [e]	AD	~100	34	2.42		Lower reference value: 2.89	nd	NS	🧍	C
	Cognitive Impaired-not demented		10	2.94						
	Normal		13	2.00						
Scileppi, 1984	AD	nd	55	44.9	6.3 (SE)	≥105	nd	NS	🧍🧍	C
	Normal and other dementias [f]	nd	58	38.2	2.4 (SE)					
Malaguarnera, 2004 [g]	AD	73	22	12.9	2.7		nd	NS	🧍	C
	Normal	74	24	14.2	2.0					
Coimbra, 2003	PD	68	31	6.25	1.5		nd	NS	🧍🧍	C
	Dementia	78	10	6.01	2.3					
Woitalla, 2004	PD [h]	65	83	18.7	6.7		nd	NS	🧍🧍🧍	C
	Normal	68	44	19.2	8.7					
Scileppi, 1984	AD	nd	55	44.9	6.3 (SE)	≥105	nd	NS	🧍🧍	C
	Normal and other dementias	nd	58	38.2	2.4 (SE)					

PLP, pyridoxal-5'-phosphate (active coenzyme form of B6); VD, Vascular Disease; RR, Risk ratio; CI, confidence interval

[a] OR for low PLP (<6.18 ng/mL): 12.3 (95%CI 1.8-84) based on logistic regression model adjusted for age, gender, RBC folate, plasma B12, serum creatinine, serum TSH, plasma homocysteine.
[b] Retrospective cohort; vitamin B6 was assessed by a protozoological assay.
[c] Adjusted for age, sex, education, baseline physical function, and smoking. Confidence interval does not agree with point estimate. Upper estimate reported as 1.07.

[d] In age- and sex-adjusted analysis, there was significant trend for increasing risk of poor cognitive function (being in the bottom quartile of baseline total cognitive score) with decreasing B6 (*P* for trend 0.002).
[e] Five additional subjects had vascular dementia and 1 PD (PLP levels not given for these patients). B6 deficiency was present in 85% of normal centenarians, 50% of cognitively impaired not-demented, and 64.7% of AD. Among patients with vascular dementia, 40% had B6 deficiency.
[f] Normal and other dementias: normal (intellectually intact, n=10), multi-infarct dementia (n=28), other dementias (n=8), and depression (n=12).
[g] 22 additional patients with vascular dementia were not included in the analysis.
[h] Total PD patients 83; PD patients with CC allele: 38, PD patients with CT allele: 12, PD patients with TT allele: 33.

Cobalamin (Vitamin B12) Level Association Studies

Study Descriptions. Seven longitudinal studies examined the potential association of serum B12 levels with the risk for developing dementia, AD, or cognitive decline (Table 28).[18,25,96,112-115] Two of the longitudinal studies recruited participants with normal cognitive function and tried to correlate cognitive function after 3 and 8 years of follow-up to the baseline levels of vitamin B12.[96,114] Cognitive function in these two studies was assessed by MMSE score, as well as by tests on construction praxis, language, working and recall memory, and visual reproduction. Sample size ranged between 234 and 1092 among the studies. Six studies included cognitively intact subjects while the seventh also recruited patients with AD. Follow-up ranged between 20 months and 8 years. Studies were generally of moderate quality (5 B, 2 C) and broad applicability.

Four cross-sectional studies assessed the potential association between B12 serum levels and cognitive function (Table 29).[83,116-118] Sample size ranged from 127 to 680. One study included patients with AD and frontotemporal dementia, another study had patients with PD and normal individuals while two studies recruited only subjects with AD. All studies implemented MMSE to assess cognitive function. In addition one study used ADAS test while another used Mattis' DRS. Studies were of low to moderate quality (2 B, 2 C) and narrow to broad applicability.

There were 22 additional studies that compared the B12 serum levels between different groups of participants.[99,106,107,111,119-136] Two of the longitudinal studies also compared mean B12 levels with AD diagnosis and cognitive function at baseline.[25,113] Five studies estimated the odds ratio for AD or cognitive impairment at certain B12 serum levels (Table 30).[120,121,123,127,130] Nine studies compared the percentage of participants with low serum B12 level among different groups including subjects with dementia, cognitive impairment, AD, vascular dementia, and cognitively intact individuals (Table 31).[25,119,121,122,124,125,129,133,134] Definitions of low B12 level varied among studies, ranging from ≤139 mg/mL to <340.1 mg/mL. In addition, 19 studies compared the mean B12 serum levels between different groups of participants, such as subjects with dementia, cognitive impairment, AD, senile and vascular dementia, PD, and cognitively intact individuals (Table 32).[99,106,107,111,113,120,122-132,134,135] Sample size ranged from 41 to 939. All studies measured serum B12 levels except for one study that reported also CSF B12 levels.[124] Studies were of low to moderate quality (1 A, 7 B, 14 C) and narrow to broad applicability.

Overall Effect. None of the longitudinal studies showed any significant correlation between serum B12 levels and the risk for developing AD or dementia. However, Tucker 2005, after adjusting for baseline cognitive measures, age, education, smoking, alcohol intake, BMI, diabetes, systolic blood pressure, time of second measure relative to folic acid fortification, time interval between the two cognitive measures, and serum creatinine, reported a significant correlation between higher levels of vitamin B12 at baseline and better performance in the figure

copying test after 3 years of follow-up (β=0.56, P <0.05). Similarly, Elias 2005, after adjusting for age, education, and gender as well as for Framingham stroke risk profile score, creatinine, alcohol consumption, coffee consumption, total cholesterol, BMI, and ApoE genotype described a significant correlation between higher levels of vitamin B12 at baseline and better performance in the global composite score for cognitive function after almost 8 years of follow-up (β=0.002, P <0.05). This study also reported significant correlation for immediate and delayed recall in the visual reproduction test (β=0.04, P<0.02 and β=0.04, P<0.03 respectively).

Among the other studies that evaluated cognitive function, no significant correlation was found between B12 serum levels and cognitive function test scores for any of the populations included. Among the studies that estimated OR, only Argyriadou 2001 found that the odds for low B12 serum level is two-fold higher in subjects with MMSE score low enough to show cognitive impairment than in cognitively intact individuals (P=0.03). The cutoff level for low B12 in this paper was <145 mg/mL. There were two more studies, which did not estimate an OR, but reported that significantly more subjects with AD or cognitively impaired presented with low serum B12 levels. Tripathi 2001 compared patients with AD and low B12 levels (<187 mg/mL) and subjects with other types of dementia (P<0.05) while Shahar 2001 compared cognitively impaired subjects presenting with lower B12 levels (<203 mg/mL) and cognitively impaired subjects with higher B12 levels (one group with B12 levels 150 to 250 mg/mL and another with greater than 250 mg/mL) (P=0.04 after adjusting for age).

Clarke 1998 compared mean serum B12 levels between patients with AD and cognitively intact participants and found no significant difference. However, when the same study was restricted only to the population with a histological diagnosis of AD, it found that significantly lower serum B12 levels were measured compared to the normal population (P<0.05). A subgroup of the participants in the same study, including 51 subjects with histological diagnosis of AD and 65 normal participants, was evaluated in a later publication by Refsum 2003. Serum holotranscobalamin levels, an active part of total serum B12, were measured and were found to be significantly lower in patients with AD than in controls (P<0.001).

Postiglione 2001 also found significantly lower B12 levels in patients with AD compared to normal individuals but the difference was not significant when the analysis was adjusted for age, serum creatinine, and duration of AD. In addition Religa 2003 reported significantly lower serum B12 levels in the AD group compared to cognitively intact participants (P<0.05). In the same study, no significant difference was reported when subjects with mild cognitive impairment were compared with the normal population. Tripathi 2001 also compared subjects with AD and patients with other dementias and found that the AD population presented with significantly lower B12 levels. In contrast Regland 1988 found that mean vitamin B12 levels for AD and cognitively intact groups were normal while the senile dementia group had a significantly lower B12 level (P=0.0002). None of the other studies including populations with AD or cognitive impairment supported any significant differences for B12 levels. Studies with subjects presenting with PD and vascular dementia did not report any significant results.

Interactions and Covariates. Prospective longitudinal studies reached statistical significance less often than cross-sectional studies. When they reported significant associations, both longitudinal and cross-sectional studies usually found that better cognitive function was related to higher vitamin B12 levels. Assantachai 1997 found that patients with AD and ApoE ε4 genotype had significantly lower B12 levels than patients with vascular dementia and ApoE ε4 genotype, while AD patients with other genotypes had similar B12 levels as those with vascular dementia.

Woitalla 2004 examined the correlation of B12 levels and diagnosis of PD in patients with different MTHFR C677T genotypes (CC, CT, TT). No significant difference was reported when the three genotype groups were compared to each other or to the non-PD participants. McCaddon 2004 found that holotranscobalamin was significantly higher in CC genotypes than the heterozygous CG genotype (P=0.04). Postiglione 2001 also found non-significant differences in B12 levels when they analyzed subcategories of AD patients or controls who were homozygous for MTHFR C677T or non-homozygous.

Postiglione 2001 also reported a statistically significant correlation between duration of disease in months and B12 ($r = –0.460$, $P<0.05$), supporting a decrease in B12 vitamin levels with longer AD duration. Anello 2004 reported that B12 levels were not influenced by other covariates such as the severity of dementia or age of onset of the disease. Refsum 2003 showed that low holotranscobalamin was associated with AD at high total homocysteine concentrations (OR 9.45), but not at low homocysteine concentrations.

There was no evidence across studies of differences in association with tests of different cognitive domains.

Summary. Thirty-three studies of low to moderate quality and narrow to broad applicability investigated a potential association between serum or CSF vitamin B12 levels and cognitive function, or diagnosis of several types of dementia and cognitive impairment. Most of the studies focused on AD. The threshold values to define low B12 levels varied across studies. Based on the very few longitudinal studies, vitamin B12 levels did not affect the risk for developing AD or dementia. However, one of the longitudinal studies reported a significant correlation between higher levels of vitamin B12 at baseline among cognitively intact subjects and better performance in the figure copying test after 3 years of follow-up. Another longitudinal study also described a similar correlation for the global composite score for cognitive function and the immediate and delayed recall in the visual reproduction test after almost 8 years of follow-up. However, the clinical importance of these results is unclear. The existing evidence from other studies, which implemented a cognitive function assessment instrument, did not support any correlation between vitamin B12 levels and cognitive function. Among cross-sectional studies, there was a trend for vitamin B12 levels to be lower in patients with AD or other types of dementia, which in certain studies reached statistical significance. However, this trend was not consistent. An inverse correlation between vitamin B12 levels and duration of AD was reported by one study. Besides that evidence for patients with AD or cognitive impairment, there was very limited evidence for populations with PD, and vascular dementia. Potential factors such as genetic mutations, or disease severity that may affect vitamin B12 levels were analyzed by few studies without a consistent effect. Considering also that most of the studies were cross-sectional, no causal relation between B12 vitamin and the developing or progression of dementia can be established.

Table 28. Association of serum vitamin B12 levels with diagnosis of AD, dementia, or cognitive decline in longitudinal studies

Author Year	Baseline Population	Baseline Mean Age (yr)	N	Follow-up	B Vitamin Level Threshold (pg/mL)	Outcomes	Results		Applicability	Quality
Ravaglia, 2005	Normal	73.6	937	Mean 3.8 yr	<340.1	Newly diagnosed dementia	HR 0.8 (95% CI 0.6-1.2) [a]		🧍🧍	B
						Newly diagnosed AD	HR 0.7 (95%CI 0.4-1.1) [a]			
Elias, 2005	Normal	≥60	705	Mean 7.6 yr	Mean 447	Global composite score ↑	β 0.002 [b]	*P*<.05	🧍🧍🧍	B
						Visual reproductions-immediate recall ↑	β 0.036 [b]	*P*<.02		
						Visual reproduction-delayed recall ↑	β 0.041 [b]	*P*<.03		
Wang, 2001	MMSE ↑ ≤ 26	75-101	370	3 yr	≤203	Newly diagnosed AD	Unadj: RR 1.7 (95% CI 0.9-3.1) Adj [c]: RR 1.6 (95% CI 0.9-2.8)		🧍🧍🧍	B
	MMSE ↑ > 26				>203	Newly diagnosed dementia	Unadj: RR 1.4 (95% CI 0.8-2.4) Adj [c]: RR 1.3 (95% CI 0.7-2.3)			
Kado, 2005	Normal	74	370	7 yr	<294.1 ≥294.1	Increased risk of cognitive decline [d]	RR 1.4 (95%CI 0.9-2.1) [e]		🧍🧍	B
Tucker, 2005	Normal	67	315 [f]	Mean 1092 days	Range: 122-1449	MMSE ↑	β -0.16 [g]	NS	🧍🧍	B
						Construction praxis: spatial copying, sum of drawings ↑	β 0.56 [g]	*P*<.05		
						Language: verbal fluency ↑	β 0.06 [g]	NS		
						Working memory: backward digit span, longest span recalled ↑	β 0.18 [g]	NS		
						Recall memory: word lists, total of 3 trials ↑	β -0.20 [g]	NS		
Seshadri, 2002	Normal	76	1092	Median 8 yr	nd	Newly diagnosed AD; newly diagnosed dementia	After adjusting for age, sex, and ApoE genotype B12 levels were not independently related to the risk of dementia or AD		🧍🧍🧍	C

Continued

Table 28. Association of serum vitamin B12 levels with diagnosis of AD, dementia, or cognitive decline in longitudinal studies (Continued)

Author Year	Baseline Population	Baseline Mean Age (yr)	N	Follow-up	B Vitamin Level Threshold (pg/mL)	Outcomes	Results	Applicability	Quality
Bowirrat, 2002	AD	nd	76	Mean 20 mo	nd	Newly diagnosed AD	Subjects in the lowest B12 tertile did not have greater risk to develop AD after adjustment for year of birth and gender	🚹🚹🚹	C
	Normal	nd	158						

↑ Higher score indicates better cognitive function. yr, years; mo, months; unadj, unadjusted; adj, adjusted; RR, Risk ratio; CI, confidence interval; HR, Hazard ratio; MMSE, Mini-Mental State Examination score

[a] Adjusted for age, sex, education; ApoE genotype; stroke; serum concentrations of creatinine, folate, Hcy, BMI, diabetes, cardiovascular disease, and hypertension; results non significant.
[b] Adjusted for age, education, and gender (not clear if it is also adjusted for Framingham stoke risk profile score, creatinine, alcohol consumption, coffee consumption, total cholesterol, BMI, and ApoE genotype).
[c] Adjusted for age sex and education; both unadjusted and adjusted RR were non significant.
[d] Defined as 7 year cognitive change ≥ 9-point drop (worst quartile).
[e] Adjusted for age, sex, education, baseline cognitive function, baseline physical function, and smoking; results non significant.
[f] For MMSE, N=271-275; for construction praxis, N=280-284; for language, N=239-243; for working memory, N=236-240; and for recall memory, N=235-239.
[g] Adjusted for baseline cognitive measures, age, education, smoking, alcohol intake, BMI, diabetes, systolic blood pressure, time of second measure relative to folic acid fortification, time interval between the two cognitive measures, and serum creatinine.

Table 29. Association of serum vitamin B12 levels with cognitive function in cross-sectional studies

Author Year	Population	Mean Age (yr)	N	B Vitamin Level (pg/mL)				Test / Subtest	Results			Applicability	Quality
				Mean	SD	Normal Range	*P*		Mean Cognitive Score	r	*P*		
Whyte, 2002	AD AD	79 75	37 643	≤ 200 ≥ 201	nd	≥ 201	nd	MMSE ↑	14.7 16.9	nd	NS	🚹🚹🚹	B
Clarke, 2003	PD Normal	75 nd	83 44	nd	nd	nd	nd	MMSE ↑	nd	Unadj: - 0.1 Adj: -0.05 [a]	NS	🚹🚹	B
Engelborghs, 2004	AD FTD	79 69	152 28	383 317	258 120	193-982	nd	MMSE ↑	nd		NS	🚹🚹	C
Stuerenburg, 2004	AD	72	241	371	216	nd	nd	MMSE ↑	nd		NS	🚹	C
Clarke, 2003	PD Normal	75 nd	83 44	nd	nd	nd	nd	ADAS cognitive ↓	nd	Unadj: - 0.1 Adj: 0.04 [a]	NS	🚹🚹	B
Whyte, 2002	AD AD	79 75	37 643	≤ 200 ≥ 201	nd	≥ 201	nd	Mattis DRS ↑	105.4 110.8	nd	NS	🚹🚹🚹	B

↑ Higher score indicates better cognitive function. ↓ Lower score indicates better cognitive function. FTD, Fronto Temporal Dementia; MMSE, mini-mental status examination; ADAS cognitive, Alzheimer's Disease Assessment Scale-Cognitive; Mattis DRS, Mattis' Dementia Rating Scale

[a] Adjusted for age.

Table 30. Studies reporting odds ratio (OR) or risk ratio (RR) for diagnosis of AD or cognitive impairment at threshold vitamin B12 serum levels

Author Year	Population	Mean Age (yr)	B Vitamin Level (pg/mL)	N	OR /RR	95% CI	*P*	Applicability	Quality
Mizrahi, 2004	AD Normal	74 75	276 - 352 <276	230	0.7 [a] 1.3 [a]	0.3, 1.9 0.5, 3.4	NS	🚹🚹🚹	A
Quadri, 2004	Cognitively impaired Normal	76	317 - 411	81	0.8 [b]	0.3, 2	NS	🚹🚹🚹	B
	AD Normal	79 76	317 - 411	74	0.6 [b]	0.2, 1.7	NS		
	Cognitively impaired Normal	76	<317	81	1.0 [b]	0.4, 2.4	NS		
	AD Normal	79 76	<317	74	0.8 [b]	0.3, 2	NS		
Anello, 2004	AD Normal	71 70	nd	361	1.0	0.99, 1.01	NS [c]	🚹🚹	B
Clarke, 1998 Refsum 2003	AD Normal	73	271- 379 <271	272	1.3 [a] 1.7 [d] 1.4 [a] 1.4 [d]	0.8-2 1-3 0.9-2.2 0.8-2.5	NS	🚹🚹	B
	AD (histological diagnosis) Normal	78 73	271- 379 <271	184	2.1 [a] 5.6 [d] 1.8 [a] 4.3 [d]	1.2-3.6 2.6-11.9 1.0-3.2 2.1-8.8	NS		
Argyriadou, 2001	MMSE ⇑ ≤ 24 MMSE ⇑ > 24	≥65	<145	536	2.0 [e]	1.1, 4.0	.03	🚹🚹	C
Kado, 2005	Participants in the bottom quartile of total cognitive score Participants not in the bottom quartile of total cognitive score	74	<294.1 ≥294.1	499	1.2 [f]	0.8-1.7	NS	🚹🚹	B

⇑ Higher score indicates better cognitive function. MMSE, mini-mental status examination.

[a] Adjusted for age and sex.
[b] Adjusted for age, sex, education and creatinine.
[c] Results were remained NS also with a multivariate analysis adjusted for MTHFR, ApoE ε4, and TCN1 genotypes, and homocysteine level (and other B vitamin); B12 levels were not influenced by the severity of dementia or age of onset of the disease.
[d] Adjusted for age, sex, smoking, social class, and ApoE ε4 genotype.
[e] Adjusted for age, intake site, and anemia (and other B vitamins).
[f] Adjusted for age, sex, education, baseline physical function, and smoking.

Table 31. Studies reporting prevalence of subjects with threshold serum vitamin B12 levels among those with dementia diagnoses

Author Year	Population	Mean Age (yr)	N	B Vitamin Level (pg/mL)	Normal Range	% Subjects	*P*	Applicability	Quality
Wang, 2001	MMSE ⇑ ≤ 26	75-101	173	≤203	nd	17.3	NS	🧍🧍🧍	B
	MMSE ⇑ > 26		197			14.2			
				≤339	nd	52.6	NS		
						42.6			
Cacabelos, 2004	AD	71	465	<150	≥150	4	NS	🧍🧍	B
	Vascular dementia	70	474			3			
Postiglione, 2001	AD	68	74	<179	179-1132	5	nd	🧍🧍	B
	Normal	nd	74			0			
Gottfries, 2001 [a]	AD	70	≤43	<203	≥203	0	nd	🧍🧍🧍	C
	Mild cognitive impairment		≤32			6.3			
	Vascular dementia		≤14			7.7			
	Subjective memory complaints		≤12			8.3			
Argyriadou, 2001	MMSE ⇑ ≤ 24	≥65	245	≥145	≥145	37.9	NS	🧍🧍	C
				<145		55.4			
	MMSE ⇑> 24			≥145		62.1	nd		
				<145		44.6			
	MMSE ⇑ ≤ 24 (men)	≥65	245	≥145	≥145	34.8	.008		
				<145		62.5			
	MMSE ⇑ > 24 (men)			≥145		65.2	nd		
				<145		37.5			
	MMSE ⇑ ≤ 24 (women)	≥65	291	≥145	≥145	40.5	NS		
				<145		50.0			
	MMSE ⇑ > 24 (women)			≥145		59.5	nd		
				<145		50.0			
Joosten, 1997	AD	83	52	<139	140-550	3.8	NS	🧍🧍	C
	Normal (hospitalized)	81	50			10.0			
	Normal (non hospitalized)	79	49			6.1			
Tripathi, 2001	AD	62	38	<187	187-1057	39.5	<.05	🧍🧍	C
	Other dementia [b]	60	62			12.9			
Shahar, 2001	Cognitively impaired	78	238	<203	>338.8	46.9	Unadj: NS	🧍	C
				150 - 250		36.4	Adj: .04 [c]		
				>250		35.7			

⇑ Higher score indicates better cognitive function. MMSE, mini-mental status examination; unadj, unadjusted; adj, adjusted

[a] 101 participants in total cohort (43+32+14+12); for plasma B12, N=99.
[b] Other dementia included mixed, diffuse Lewy body disease, infections, nutritional, head injury, systemic, extra-pyramidal, etc.
[c] Adjusted for age.

Table 32. Association of serum and CSF vitamin B12 levels with diagnoses of dementias in cross-sectional studies

Author Year	Population	Mean Age (yr)	N	B Vitamin Level (pg/mL) Mean	SD	Normal Range	*P*	Applicability	Quality
Mizrahi, 2004	AD	74	75	323	136	≥169	NS	🧍🧍🧍	A
	Normal	75	155	351	175				
Quadri, 2004	AD	79	74	381	111	nd	NS	🧍🧍🧍	B
	Cognitively impaired	76	81	373	117				
	Control		55	377	99				
Assantachai, 1997	Cognitively impaired	69	51	460	488	nd	NS [a]	🧍🧍🧍	B
	Normal		108	408	184				
Cacabelos, 2004	AD	71	465	488	328	≥150	NS	🧍🧍	B
	Vascular dementia	70	474	521	505				
Anello, 2004	AD	71	180	377	221	nd	NS	🧍🧍	B
	Normal	70	181	283	211				
Clarke, 1998 Refsum 2003	AD	73	164	236	112	nd	NS	🧍🧍	B
	Normal		108	253	100				
	AD (histological diagnosis)	78	76	215	79	nd	<.05		
	Normal	73	108	253	100				
Postiglione, 2001	AD	68	74	689	301	179-1132	Unadj: <.001 Adj: NS [b]	🧍🧍	B
	Normal	nd	74	701	234				
Regland, 1988	AD	59	35	432	179	nd	.0002	🧍	B
	Senile dementia	75	56	333	214				
	Control	72	54	454	249				
Religa, 2003	AD	74	99	317	140	157-1059	<.05	🧍🧍🧍	C
	Normal	71	100	414	241				
	Mild cognitive impairment	71	98	386	159		NS		
	Normal		100	414	241				
Bowirrat, 2002	AD	nd	76	nd	nd	nd	NS	🧍🧍🧍	C
	Normal	nd	158	nd	nd				

Continued

Table 32. Association of serum and CSF vitamin B12 levels with diagnoses of dementias in cross-sectional studies (Continued)

Author Year	Population	Mean Age (yr)	N	B Vitamin Level (pg/mL)				Applicability	Quality
				Mean	SD	Normal Range	*P*		
Woitalla, 2004	PD	65	83	371	218	nd	NS	🧍🧍🧍	C
	Normal	58	44	418	233				
McCaddon, 2004	AD	79	121 [c]	333	nd	nd	NS [d]	🧍🧍🧍	C
	Normal			342	nd				
Gottfries, 2001 [e]	AD	70	≤43	356	177	203 - 949	NS	🧍🧍🧍	C
	Mild cognitive impairment		≤32	296	127				
	Vascular dementia		≤14	272	143				
	Subjective memory complaints		≤12	330	154				
	AD	70	≤43	13.9	13.6	CSF: nd	NS	🧍🧍🧍	C
	Mild cognitive impairment		≤32	11.3	7.9				
	Vascular dementia		≤14	10.8	8.5				
	Subjective memory complaints		≤12	14.4	8.7				
Nilsson, 1996	Dementia [f]	75	68	323	136	149 - 881	NS	🧍🧍	C
	Normal		163	351	175				
Joosten, 1997	AD	83	52	284	nd	140-550	NS	🧍🧍	C
	Normal (hospitalized)	81	50	281	nd				
	Normal (non hospitalized)	79	49	284	nd				
Scileppi, 1984	AD	nd	55	290	31 (SE)	≥105	NS	🧍🧍	C
	Normal and other dementias [g]	nd	58	533	25 (SE)				
Tripathi, 2001	AD	62	38	263	168	187-1057	<.05	🧍🧍	C
	Other dementia [h]	60	62	289	139				
Coimbra, 2003	PD	68	31	356	261	nd	NS	🧍🧍	C
	Dementia w/o Stroke	78	10	441	323				
Ravaglia, 2003	MMSE ↑ 24-25	~100	46	233	nd	≥201	NS	🧍	C
	MMSE ↑ 26-28		259	240	nd				
	MMSE ↑ > 28		345	237	nd				

↑ Higher score indicates better cognitive function. CSF, Cerebrospinal fluid; MMSE, mini-mental status examination; unadj, unadjusted; adj, adjusted.

[a] Patients with AD and ApoE 2/4 (n=4 or 6) had significantly lower B12 level (364±141 pg/mL) than patients with vascular dementia and ApoE 2/4 (n=9; 678±365 pg/mL; $P < 0.04$); AD patients with other genotypes had similar B12 levels as their counterparts with vascular dementia.

[b] Adjusted for age, serum creatinine, and duration of AD; also NS differences in B12 levels by subcategories of cases or controls who were homozygous for MTHFR C677T or non-homozygous; statistically significant correlation between duration of disease (months) and B12 ($r = –0.460$, $P < 0.05$).
[c] Initially AD:70 and Normal: 74 but 23 subjects were excluded from the analysis because they received B12 supplementation; unclear how many of the excluded subjects were in the AD or in the Normal group.
[d] Results also for holotranscobalamin levels were NS.
[e] 101 participants in total cohort (43+32+14+12); for plasma B12, N=99.
[f] AD, frontotemporal dementia and other dementia including alcohol and brain tumor dementia.
[g] Normal (intellectually intact, n=10), multi-infarct dementia (n=28), other dementias (n=8), and depression (n=12).
[h] Other dementia included mixed, diffuse Lewy body disease, infections, nutritional, head injury, systemic, extra-pyramidal, etc.

Folate Level Association Studies

Study Descriptions. A total of 34 studies examined the role of folate vitamin levels with the diagnoses of age related neurocognitive disorder or with cognitive function. Twenty-three studies examined the mean folate level with cognitive function or PD,[83,99,105-107,109,111,113,116,120,122-125,127-132,137-139] 10 examined the prevalence of folate deficiency in normal and cognitively impaired or demented participants,[25,114,119,121,122,124,125,129,140,141] and 15 assessed the risk of AD, dementia, and cognitive impairment with folate levels.[18,25,96,105,112-115,120,121,123,127,130,140,142] Ten of the studies were longitudinal, examining the association between folate levels and future cognitive function; the remainders were case-control or cross-sectional with single time-point analyses (Table 33). The folate levels were assessed in the RBC, plasma, serum, CSF, and blood. The sample sizes of the studies ranged from 30 to 1,100. The majority of the studies were graded moderate to poor quality (1 A, 15 B, 18 C). Fifteen studies had broad, 17 moderate, and 2 narrow applicability.

Overall Effect. All studies reported lower mean folate levels or higher prevalence of folate deficiency among subjects with AD, and cognitive impairment. Among studies that assessed the association between folate levels and cognitive function, four longitudinal studies and one case-control study reported a statistically significant association between lowest quantile of folate level and cognitive decline after adjusting for possible confounders. One other case-control study reported a significant inverse association of folate with cognitive function. Two studies reported folate levels within normal limits among PD subjects.

Fewer than one-third of the 23 studies that examined the mean folate levels and cognitive function reported significantly lower mean folate levels in AD compared with normal subjects (Table 33). Only two studies – Postiglione 2001 and Bowirrat 2002 – adjusted mean folate levels for possible confounders; they reported no significant differences in mean folate levels between AD and normal subjects.

All studies that examined the prevalence of folate deficiency compared subjects with AD or cognitively impairment with other types of dementia or normal subjects (Table 34). The range of prevalence of folate deficiency was between 0 and 67 percent. Across all studies, the prevalence of folate deficiency was higher among AD than controls. Only two studies, Joosten 1997 and Wang 2001 reported statistically significant prevalence of folate deficiency among AD subjects, and those with MMSE mean score ≤26, respectively.

Among 10 studies that examined the longitudinal decline of cognitive function (Table 35), Ravaglia 2005, Kado 2005, Tucker 2005, Maxwell 2002, and Clarke 1998 compared the lowest versus the highest quantile of folate. After adjusting for possible confounders, Ravaglia 2005, Kado 2005, and Tucker 2005 found an increased risk of cognitive function decline among those

in the lowest quantile levels of folate. Tucker 2005 found independent effects of lowest folate level among men with mild cognitive impairment with longitudinal (mean of 3 year) and large decline in the score of constructional praxis (spatial copying). Maxwell 2002 examined the risk of adverse health outcomes including cognitive decline with association to the quartiles of folate during 5-year follow-up. This study noted that subjects with lowest folate levels were at greater risk for significant cognitive decline independent of possible confounders. In contrast, Seshadri 2002, Elias 2005 and four other longitudinal studies found no association between folate level and future cognitive function. Three case-control and one cross-sectional studies assessed the odds of AD in relation to high versus the low levels of folate, using a single time point analyses (Table 36). Of note, Quadri 2004 reported a consistently significant association of cognitive impairment with the lowest tertile of folate.

Snowdon 2000, a case-control study described a significant negative age-adjusted correlation of folate levels with severity of cerebral cortex atrophy among all AD subjects, as well as a subset of AD subjects with histologically significant cerebral cortex lesions at autopsy. The regression analysis adjusted for age and histological severity of AD found a 4.4 ng/mL decrease in serum folate was associated with a 1-point decrease for the MMSE score indicating a significant inverse association of folate with cognitive function.

Two studies reported folate levels in PD subjects (Table 33). Woitalla 2004 compared the mean folate level in PD with normal subjects. This study subdivided PD and normal subjects according to their methylene tetrahydrofolate reductase (MTHFR) genotypes CC, CT, TT. The folate levels did not differ between PD and normal subjects, but was significantly higher in the CT allele subgroup of PD compared with normal subjects. Coimbra 2003 reported folate levels within the normal range that did not differ between PD and dementia subjects.

Interactions and Covariates. About one-third of the studies reported associations of folate levels with cognitive function decline adjusted for possible confounders. Four longitudinal studies that adjusted for all possible confounders reported independent and statistically significant association between folate level and cognitive function. Across the studies, there was an association between folate level and global cognitive function. Only one study[96] reported significant effect on one other cognitive domain.

Summary. There are 34 studies of moderate to poor quality that have examined the role of folate vitamin levels with the diagnoses of age related neurocognitive disorder or with cognitive function. Overall, the studies reported lower mean folate levels or higher prevalence of folate deficiency among AD and cognitive impaired subjects. One-third of the studies adjusted for possible confounders. Of note, four of the 10 longitudinal studies reported consistent and statistically significant association between folate level and cognitive function score. Two case-control studies reported greater risk of cognitive function decline with lower folate levels among AD subjects. Two studies reported mean folate levels within normal limits among PD subjects.

Table 33. Association of mean folate levels with diagnosis of age-related neurodegenerative disease

Author Year	Population	Mean Age (yr)	N	Tissue	Folate Level (ng/mL) Mean	SD / range	Normal Range	*P*	Applicability	Quality
Mizrahi 2004	AD	~80	75	Plasma	1.9	1.4	>1.6	NS	🚹🚹🚹	A
	Normal	~77	155		2.1	1.1				
Quadri 2004	AD	79	74	Serum	6.0	2.5	nd	.04	🚹🚹🚹	B
	Cognitive impaired	76	81		6.2	2.6		.04		
	Normal	76	55		7.5	2.6				
Assantachai 1997	Cognitive impaired	69	44	RBC	416	123	nd	NS	🚹🚹🚹	B
	Normal	69	103		399	143				
Cacabelos 2004	AD	71	465	Blood	6.1	2.8	>3.0	NS	🚹🚹	B
	Vascular dementia	70	474		6.3	3.1				
Anello 2004	AD	71	180	Plasma	6.3	2.5	nd	.09	🚹🚹	B
	Normal	70	181		6.9	2.6				
Clarke 1998	AD (clinical diagnosis)	73	164	Serum	7.8	4.7	nd	<.001	🚹🚹	B
	AD (histological diagnosis)	77	76		6.7	4.2		<.001		
	Normal	73	108		10.1	4.4				
	AD (clinical diagnosis)	73	164	RBC	382	197	nd	<.05		
	AD (histological diagnosis)	77	76		325	170		<.001		
	Normal	73	108		437	180				
Clarke 2003	Mixed Dementia	75	98	Plasma	3.2	3.1	0.75-13.5	NS	🚹🚹	B
	Cognitive impaired	75	51		3.8	3.1				
Postiglione 2001	AD	68	74	Plasma	2.5 3.9 [a]	0.9 1.5	3.1-12.4	<.001 NS [a]	🚹🚹	B
	Normal	68	74		3.8 3.4 [a]	1.4 1.6				
Miller 2002	AD	79	32	RBC	461	159	>160	NS	🚹🚹	B
	Normal	75	22		496	212				
Snowdon 2000	AD lesions	91	15	Serum	8.8	10.2	4.8-23.8	nd	🚹	B
	AD no lesions	91	15		11.9	10.5				
Religa 2003	AD	74	99	Serum	8.5	3.4	5.3-14.4	NS	🚹🚹🚹	C
	Cognitive impaired	71	98		10.9	3.9		NS		
	Normal	71	100		7.6	5.4				
Bowirrat 2002	AD	≥60	76	Plasma	nd	nd	nd	NS [b]	🚹🚹🚹	C
	Normal	≥60	158		nd	nd				
Woitalla 2004	PD	65	83	Serum	6.4	3.3	nd	<.02 [c]	🚹🚹🚹	C
	CT allele		38		7.5	3.9				
	TT allele		12		5.5	2.8				
	CC allele		33		5.4	2.1				
	Normal	58	44		6.5	2.9				

Continued

Table 33. Association of mean folate levels with diagnosis of age-related neurodegenerative disease (Continued)

Author Year	Population	Mean Age (yr)	N	Tissue	Folate Level (ng/mL)				Applicability	Quality
					Mean	SD / range	Normal Range	*P*		
Nagga 2003	AD	75	47	Serum	84.2	75.0	33-210	<.05 [d]	🚹🚹🚹	C
	AD with CVD	76	9		72.8	89.0				
	Cognitive impaired	78	8		279	115				
	Normal	75	101		nd	nd				
Gottfries 2001 [e]	AD	70	≤43	Plasma	5.3	1.9	2.6-17.2 [f]	NS	🚹🚹🚹	C
	Mild cognitive impaired	70	≤32		6.2	3.0				
	Vascular dementia	70	≤14		5.0	2.0				
	Subjective memory complaints	70	≤12		5.6	2.3				
	AD	70	≤43	Blood	105	35	61.8-167 [g]	NS		
	Mild cognitive impaired	70	≤32		112	40				
	Vascular dementia	70	≤14		118	64				
	Subjective memory complaints	70	≤12		125	38				
Ravaglia 2003	MMSE ↑ 24-25	79	46	Serum	11.4	10.0, 13.0	2.5	NS	🚹🚹	C
	MMSE ↑ 26-28	73	259		11.3	10.7, 11.9				
	MMSE ↑ > 28	72	345		11.6	11.1, 12.2				
Nilsson 2003	Men with dementia	84	20	nd	4.1	nd	nd	NS	🚹🚹	C
	Men with intact cognition	84	83		4.8	nd				
	Women with dementia	85	66		3.6	nd		<.005		
	Women with intact cognition	85	173		4.6	nd				
Nilsson 1996	AD	75	68	Blood	57.4	58.3	55-221 [g]	<.05	🚹🚹	C
	Normal	75	163		68.8	68.8				
Engelborghs 2004	AD	79	152	RBC	246	198	93-641	NS	🚹🚹	C
	Mixed dementia	69	28		277	195				
Joosten 1997	AD	82	52	Serum	3.5	1.3, 9.7	2.4-7.2	NS	🚹🚹	C
	Non-AD [h]	81	50		4.0	1.5, 10.9		NS		
	Normal	79	49		3.8	1.8, 8.2				
Scileppi 1984	AD	nd	55	Blood	11.7	1.5	>5.0	NS	🚹🚹	C
	Normal and other dementia [j]	nd	58		10.7	1.0				
Serot 2001	AD	76	30	CSF	5.4	2.2	nd	NS	🚹🚹	C
	Normal	73	28		5.8	2.1				
	AD	76	30		8.3	1.8	nd	<.001		
	Normal	73	36		10.0	2.0				
Coimbra 2003	PD	68	31	Plasma	5.6	4.0	2-12	NS	🚹🚹	C
	Dementia w/o Stroke	78	10		4.3	2.8				

↑ Higher score indicates better cognitive function. MMSE: Mini-Mental State Exam; nd: not documented; NS: non-significant.

[a] Adjusted for age, serum creatinine, and duration of AD.
[b] Adjusted for age.
[c] PD patients with CT allele had significantly higher folic acid levels compared with others in the post hoc analysis.
[d] AD and AD with CVD had lower levels of blood folate vs cognitively impaired.
[e] Total cohort =101 (43+32+14+12). However, plasma folate had N=98 and blood folate had N=74.
[f] Plasma folate.
[g] Blood folate.
[h] Hospitalized.
[j] Normal (intellectually intact, n=10), multi-infarct dementia (n=28), other dementias (n=8), and depression (n=12).

Table 34. Prevalence of folate deficiency among subjects with dementia, cognitive impairment, and normal cognition

Author Year	Population	Mean Age (yr)	N	Tissue	Folate Level (ng/mL)	Normal range	% Deficient	P	Applicability	Quality
Elias 2005	Normal	60-82	705	Plasma	<3.1	nd	12.1		🚹🚺🚹	B
Wang 2001	MMSE ↑ ≤ 26	75-101	54	Serum	≤4.4	>4.4	22.1	<.01	🚹🚺🚹	B
	MMSE ↑ > 26				≤4.4		8.2			
	MMSE ↑ ≤ 26		105		≤5.3	>5.3	35.5	<.01		
	MMSE ↑ > 26				≤5.3		22.4			
Cacabelos 2004	AD	71	465	Blood	<3.0	>3.0	5	NS	🚹🚺	B
	Vascular dementia	70	474				6			
Stewart 2002	Cognitive impaired	65	61	Serum	<3.2	nd	36.1	NS	🚹🚺	B
			61		3.2-4.5		23.0			
			59		4.6-5.9		30.5			
			58		>5.9		22.4			
Maxwell 2002	AD [a]	80	49	Serum	<2.2-5.3	nd	33.3	nd	🚹🚺	B
					>6.2-15.9		20.9			
	Dementia [a]		66		<2.2-5.3		38.1			
					>6.2-15.9		24.3			
	Cognitive impaired [b]		87		<2.2-5.3		43.5			
					>6.2-15.9		29.7			
Postiglione 2001	AD	68	74	Plasma	<3.1	3.1-12.4	20	nd	🚹🚺	B
	Normal		74				0			
Argyriadou 2001	Cognitive impaired (all)	65-85	213	nd	≥1.8	≥1.8	39.5	NS	🚹🚺🚹	C
					<1.8		46.7			
	Normal (all)		315		≥1.8		60.3			
					<1.8		53.3			
	Cognitive impaired men		92		≥1.8	≥1.8	37.7			
					<1.8		33.3			
	Normal men		153		≥1.8		62.3			
					<1.8		66.7			
	Cognitive impaired women		121		≥1.8	≥1.8	41.1			
					<1.8		55.6			
	Normal women		170		≥1.8		58.9			
					<1.8		44.4			

Continued

Table 34. Prevalence of folate deficiency among subjects with dementia, cognitive impairment, and normal cognition (Continued)

Author Year	Population	Mean Age (yr)	N	Tissue	Folate Level (ng/mL)	Normal range	% Deficient	P	Applicability	Quality
Gottfries 2001	AD	70	43	Plasma	<2.6	2.6-17.2	0	NS	↑↑↑	C
	Cognitive impaired		32				6.3			
	Vascular dementia		14				7.7			
	Subjective memory complaints		12				0			
	AD	70	43	RBC	<62	62-168	5.9	NS		
	Cognitive impaired		32				4.2			
	Vascular dementia		14				0			
	Subjective memory complaints		12				0			
Joosten 1997	AD	83	52	Serum	<2.4	2.4-7.2	21.2	.04	↑↑	C
	Normal (non hospitalized)		49				6.1			
Andersen-Ranberg 2001	Dementia	100	105	Serum	B 12 / folate deficiency	nd	9	nd	↑	C
	Normal		91				11			

↑ Higher score indicates better cognitive function. MMSE: Mini-Mental State Exam; NS: non-significant.

[a] Incident cases.
[b] 3 year decline.

Table 35. Folate level as a predictor of cognitive function in longitudinal studies

Author Year	Baseline Population	Mean Age (yr)	N	Follow-up (yr)	Tissue	B Vitamin Level Threshold (ng/mL)	Outcomes	Results OR	95% CI	*P*	Applicability	Quality
Elias, 2005	Normal	≥60	705	7.6	Plasma	<3.1	Cognitive performance	Folate level was not related to cognitive function			†††	B
Wang 2001	MMSE $\bar{1}$ ≤ 26	75-101	12	3	Serum	≤4.4	AD (incident)	1.8 (unadj) [a]	1.0, 3.4		†††	B
			47			>4.4		1.7 (adj) [b]	0.9, 3.2			
	MMSE $\bar{1}$ > 26		15			≤4.4	Dementia (incident)	1.7 (unadj) [a]	1.0, 3.0			
			47			>4.4		1.6 (adj) [b]	0.9, 2.9			
Ravaglia 2005	Normal	74	937	3.8	Serum	<5.2	AD	1.95 (adj) [c]	1.15, 3.40		††	B
							Dementia	1.87 (adj) [c]	1.21, 2.89			
Clarke 1998 [d]	AD (clinical diagnosis)	73	272	4	Serum	7.6-10.7 v >10.7	AD (clinical diagnosis)	0.8 (adj 1) [e]	0.5, 1.4		††	C
								0.7 (adj 2) [f]	0.4, 1.5			
						<7.6 v >10.7		2.5 (adj 1) [e]	1.7, 3.8			
								2.3 (adj 2) [f]	1.4, 3.8			
	AD (histological diagnosis)	77	184		Serum	7.6-10.7 v >10.7	AD (histological diagnosis)	0.6 (adj 1) [e]	0.2, 1.6			
								0.4 (adj 2) [f]	0.1, 1.5			
						<7.6 v >10.7		5.0 (adj 1) [e]	3.1, 8.2			
								3.3 (adj 2) [f]	1.8, 6.3			
Kado 2005	Normal	74	370	7	Plasma	bottom quartile v top 3 quartiles	Cognitive function decline	1.71 (adj) [g]	1.13-2.37	.01	††	B

Continued

Table 35. Folate level as a predictor of cognitive function in longitudinal studies (Continued)

Author Year	Baseline Population	Mean Age (yr)	N	Follow-up (yr)	Tissue	B Vitamin Level Threshold (ng/mL)	Outcomes	Results OR	95% CI	*P*	Applicability	Quality
Tucker, 2005	Normal	67	315	~3	Plasma	11.5	MMSE ↑	β 0.12		NS	🚹🚹	B
							Construction praxis: spatial copying, sum of drawings ↑	β 1.0		<.0001		
							Language: verbal fluency ↑	β 0.76		NS		
							Working memory: backward digit span, longest span recalled ↑	β -0.28		NS		
							Recall memory: word lists, total of 3 trials ↑	β 0.43		NS		
Maxwell 2002	3MS ↑ <78	80	87	5	Serum	<2.2-5.2 v >6.2-15.9	Cognitive decline-3 yr	2.2	0.96, 4.9	NS	🚹🚹	B
			66			<2.2-5.2 v >6.2-15.9	Dementia (incident)	2.2	0.9, 5.2	NS		
			49			<2.2-5.2 v >6.2-15.9	AD (incident)	2.2	0.9, 5.5	NS		
Seshadri 2002	Cognitively intact	76	1092	8	Plasma	>6.2-15.9	Newly diagnosed AD and dementia	Folate level was not independently related to the risk of dementia or AD after adjusting for age, sex, and ApoE genotype			🚹🚹🚹	C
Bowirrat 2002	Normal	≥60	234	1.7	Plasma	Lowest v highest tertile	AD	No significant greater risk to develop AD after adjustment for year of birth and gender.			🚹🚹🚹	C
Jones 2002	Normal	≥75	230	3	nd	nd	Cognitive decline	Vitamin status and Apo E4 did not precipitate the decline			🚹🚹🚹	C

↑ Higher score indicates better cognitive function. MMSE: Mini-Mental State Exam; NS: non-significant.

[a] Relative risk.
[b] Relative risk, adjusted for age, sex, and education.
[c] Adjusted for all study covariates and homocysteine; no results reported without adjustment for homocysteine.
[d] Retrospective study.
[e] Adjusted for age and sex.
[f] Adjusted for age, sex, smoking, social class, and ApoE ε4.
[g] Adjusted for age, sex, education, baseline physical function, and smoking.

Table 36. Folate level as a predictor of cognitive function in case-control studies and cross sectional studies

Author Year	Population	Mean Age (yr)	N	Tissue	Folate Level (ng/mL)	Results OR	95% CI	*P*	Applicability	Quality
Mizrahi 2004	AD	~80	75	Plasma	3.5-5.0 v >5.0	1.3	0.5, 3.7	NS	↑↑↑	A
					<3.5 v >5.0	1.6	0.6, 4.2	<.01		
	AD (histological diagnosis)	77	184	Serum	7.6-10.7 v >10.7	0.6 (adj 1) [a]	0.2, 1.6	NS		
						0.4 (adj 2) [b]	0.1, 1.5	NS		
					<7.6 v >10.7	5.0 (adj 1) [a]	3.1, 8.2	<.05		
						3.3 (adj 2) [b]	1.8, 6.3	<.05		
Quadri 2004	AD	79	74	Serum	6.0-8.6 v >8.6	2.1 (adj) [c]	0.7, 6.4	NS	↑↑↑	B
			55		<6.0 v >8.6	3.7 (adj) [c]	1.3, 10.7	.05		
	Cognitive impaired	76	81		6.0-8.6 v >8.6	1.0 (adj) [c]	0.4, 2.8	NS		
			55		<6.0 v >8.6	3.4 (adj) [c]	1.3, 8.7	.004		
Anello 2004	AD	71	181	Plasma	nd	0.95 [d]	0.91, 1.00	.04	↑↑	B
	Normal	70	180							
Snowdon 2000	AD lesions	91	15	Serum	8.8	r = –0.80 [e]		.0006	↑	B
						r= –0.14 [f]		NS		
	AD no lesions		15		11.9	4.4 ng/mL decrease in serum folate was associated with a one-point decrease for the MMSE score ↑				
Argyriadou 2001	Cognitive impaired	65-85	536	nd	<1.8 v >1.8	3.8	0.9, 15.2	.06	↑↑↑	C

↑ Higher score indicates better cognitive function. MMSE: Mini-Mental State Exam; NS: non-significant

[a] Adjusted for age and sex.
[b] Adjusted for age, sex, smoking, social class, and ApoE ε4.
[c] Adjusted for age, sex, education, and creatinine.
[d] The lowest folate tertile compared with the highest tertile after adjusting for age, sex, education, and creatinine.
[e] Age-adjusted correlation between folate and the severity of atrophy among AD with significant histological lesions in the autopsy.
[f] Correlation with the mean number of neurofibrillary tangles in the neocortex with significant histological lesions in the autopsy.

B Vitamin-Homocysteine Interaction With Cognitive Function

Testing the hypothesis of a potential effect of the interaction between homocysteine and B vitamins on cognitive function was not the primary purpose for this report. Consequently, studies that did not consider B vitamins as independent predictors of cognitive function and limited their analyses to homocysteine or the interaction of homocysteine and B vitamins only, were not included in our review.

It is well established that B vitamin status (mostly folate, B12, and possibly B6) is a major determinant of homocysteine level.[143-145] Among elderly subjects in the Framingham study, for example, two-thirds of cases of high homocysteine were associated with at least one vitamin concentration below the 70th percentile.[143] In addition, studies have consistently found that homocysteine levels can be reduced with B vitamin treatment.[123] Furthermore, numerous studies – including several evaluated in this review of B vitamins – have demonstrated an association between higher homocysteine levels and worsened cognitive function. [18,96,114,115] Elevated homocysteine levels putatively may cause cognitive decline through both neurotoxic and vasotoxic effects.[146] Of note, almost all trials of combinations of B vitamins – and several interventions with individual B vitamins – were designed with the intent of lowering homocysteine levels. Among studies that reported data on associations between cognitive function and both B vitamins and homocysteine, most found that the association of homocysteine and cognitive function was statistically independent of B vitamin levels; thus homocysteine levels were predictive of cognitive function even after correction for B vitamin deficiency. This statistical independence was found in both cross-sectional studies [84,110,128,141] and longitudinal studies,[18,115] but does not imply a biological independence. Several studies, both cross-sectional[112,147] and longitudinal[96,114] found evidence of interactions between homocysteine and either folate, B12, or combined folate, B6, and B12.

Interpretation of the relative effect of different homocysteine levels on any interactions between B vitamin status and cognitive function is more problematic. Given that homocysteine is associated with cognitive decline and that B vitamins affect homocysteine levels, it is hypothesized that much of the B vitamins' role in preventing cognitive decline is through their effect on maintaining low homocysteine levels and thus any associations between B vitamin status and cognitive function would not be expected to be independent of homocysteine level.

However, among the five longitudinal studies that analyzed potential interactions between homocysteine and B vitamins on their association with cognitive decline, the MacArthur Studies of Successful Aging (MSSA),[112] the Conselice Study of Brain Aging (CSBA),[115] and the Veterans Affairs Normative Aging Study (VANAS)[96] each found that baseline serum folate level (and also dietary folate in VANAS) was significantly associated with various measures of cognitive decline, independent of homocysteine or vitamins B6 or B12. Each set of authors conclude that the independent contribution of low folate to cognitive impairment may affect the development of cognitive impairment through mechanisms other than homocysteine's direct neurotoxicity. Of note, VANAS found independent effects of folate only for constructional praxis (figure copying), while MSSA analyzed a summary cognitive score based on several tests and CSBA analyzed diagnosis of AD. In contrast, both the Framingham Study[18] and the Framingham Offspring Study[114] found no association between folate level and cognitive function.

B Vitamin Adverse Events

To answer the question regarding adverse events we reviewed all 39 prospective human trials of B vitamin interventions that we retrieved for possible inclusion regarding effect of treatment on age-related neurocognitive disorders. Three of these articles had multiple studies or study arms, thus there were 43 separate cohorts of subjects who received specific B vitamin treatments. Eight of these studies were rejected from analyses above either because of inclusion of ineligible populations or reporting only on outcomes not of interest for the purpose of this review.

Among the 43 studies/cohorts, only 10 reported any information on adverse events (Table 37). Only two of these reported that any adverse events occurred.

Three articles reported on adverse events related to thiamine (B1) or thiamine derivative interventions in four studies;[61,62,64] two additional studies did not report on adverse events. In three studies, there were no adverse events, among 37 subjects total who took either 3 g thiamine per day or fursultiamine 100 mg per day for 1 to 3 months. All included patients with AD. The fourth study, also of patients with AD, found that 17 subjects all tolerated well thiamine doses between 4 and 6 g per day a month at a time. Among a subset of 7 subjects who took higher doses up to 8 g per day, two reported nausea and indigestion at doses of 7.0 and 7.5 g per day, but subsequently tolerated the same dosages in later months.

The single intervention study of riboflavin (B2) did not report on adverse events.

None of 4 studies of pyridoxine (B6) reported on adverse events.

Among 18 studies of cobalamin (B12), only one reported on adverse events.[70] In a 12 week study of a cohort of 10 patients with AD who were treated with intravenous mecobalamin 500 μg 3 times a week for 8 weeks, there were no side effects detected in laboratory tests and there were no patient complaints.

Three of eight studies of folate supplementation reported on adverse events.[79,81,148] The three studies evaluated 59 subjects who took either 15 mg or 20 mg folate per day. The two studies of patients with dementia reported no adverse events over 10 weeks or an unreported duration. In a cohort study by McGeer 1972 of 18 patients with PD who were treated with 15 mg folate per day for 14 to 182 days, three reported minor symptoms of "buzzing in the ears," "a jittery feeling," or "sleeplessness." No mental changes, weight loss, or gastrointestinal symptoms were reported by patients.

One 2 year randomized trial reported that combination B6 (5 mg per day) and B12 (250 mg per day) was well tolerated in 158 healthy subjects (siblings of patients with premature atherosclerotic disease).[149]

The two studies that evaluated combination B12 and folate did not report on adverse events.

One of three studies of combination B6, B12, and folate reported on adverse events.[86] In a cohort study of 63 patients with AD who were treated with daily doses of 50 mg B6, 1 mg oral B12, and 50 mg folate, no adverse events were reported over 8 weeks.

Overall, in 10 studies that included 254 subjects taking B vitamin supplements (and 79 subjects taking placebo), two subjects with AD in one study reported mild gastrointestinal complaints with high dose thiamine, which they were later able to tolerate, and three patients with PD reported possibly neurological complaints with folate. No serious adverse events were reported.

Table 37. Reported adverse events in B vitamin intervention studies

Study, Year	Dose / Day	Popu-lation	Mean Age (yr)	Duration	Design	N Tx	N Cx	Adverse Events
Thiamine (B1)								
Meador, 1993 Study 1	3 g	AD	71	1 mo	Cross-over	17		None
Meador, 1993 Study 2	4-8 g	AD	71	13 mo [a]	Cross-over [b]	17		All tolerated doses up to 6 g/day well without any side effects 2 (of 7) subjects reported nausea and indigestion at doses of 7.0 and 7.5 g/day, but subsequently tolerated the same dosages in later months.
Blass, 1988	3 g	AD	72	3 mo	Cross-over	11		None
Mimori, 1996	Fursultiamine 100 mg	AD	72	12 wk	Cohort	9		None
Riboflavin (B2)				**No studies**				
Pyridoxine (B6)				**No studies**				
Cobalamin (B12)								
Ikeda, 1992	500 µg 3x/wk IV	AD	71	12 wk	Cohort	10		None
Folate								
Yukawa, 2001 [c]	15 mg	Dementia	56	nd	Cohort	36		None
McGeer, 1972	15 mg	PD	nd	14-182 days [d]	Cohort	18		1 buzzing in the ears, 1 jittery feeling, 1 sleeplessness. No mental changes, weight loss, or gastrointestinal symptoms.
Sommer, 2003	20 mg	Dementia	77	10 wk	RCT	5	6	None
Pyridoxine (B6) + Folate								
Vermeulen, 2005 [e]	B6: 5 mg Folate: 250 mg	Healthy	46	2 yr	RCT	68	73	None
Cobalamin (B12) + Folate				**No studies**				
Pyridoxine (B6) + Cobalamin (B12) + Folate								
Aisen, 2003	B6: 50 mg B12: 1 mg Folate: 50 mg	AD	71	8 wk	Cohort	63		None

N, number of subjects; Tx, vitamin B treatment, Cx, control;

[a] 1 month each at various doses, including 1 month of placebo.
[b] Single cohort of subjects all changing doses in a set sequence.
[c] Study did not meet eligibility criteria for evaluation of effect of B vitamin treatments.
[d] Mean 45 days.
[e] Study did not meet eligibility criteria for evaluation of effect of B vitamin treatments.

General Vitamin B Safety. As noted in Table 38, the Institute of Medicine (IOM) concludes that there are no reports of adverse events for any of the evaluated B vitamins within the range of the RDA and up to the Upper Limit (UL); although they acknowledge that data on adverse events for all the vitamins are limited.

With a few exceptions and caveats, review articles on the safety of the B vitamins have concluded that B vitamin supplementation is safe. An older review by Marks in 1989,[150] concluded that for all the B vitamins, at levels of intake approximately equivalent to those found in a good mixed diet, vitamins are beneficial and show no adverse reactions. He concluded that safe doses for thiamine are at least 50 to 100 times the RDA (i.e., above 100 mg daily); safe doses for riboflavin are substantially above 100 times the RDA (also above 100 mg daily); safe doses for pyridoxine are up to 200 mg daily (over 100 times the RDA); safe doses for oral cyanocobalamin are as high as 30 mg daily (over 10,000 times the RDA); and safe doses for folic acid of 50 to 100 times the RDA (up to about 20 mg).

The primary safety concern raised regarding thiamine involves rare reports of anaphylaxis after single oral doses in the range of 5 to 10 g or intravenous doses.[150,151] However, one reviewer, Snodgrass, in 1992 theorized, primarily based on animal studies, that high dose intravenous thiamine – generally used in patients suspected of having Wernicke's encephalopathy, in part to prevent seizures – may actually be causing seizures. However, as noted by Snodgrass, a large report of almost 1000 patients receiving intravenous thiamine rarely resulted in complications.[152] Only one patient had a major adverse reaction (generalized pruritis).

We found no safety concerns related to riboflavin.

Long-term, high-dose pyridoxine is well known to cause a reversible neuropathy. A literature review in 1986 by Cohen et al. noted that adults receiving more than 500 mg per day are at risk for developing sensory neuropathy, while short-term courses or lower daily doses does not result in adverse neurological changes.[153] However, as noted by both Marks and Snodgrass, there have been reports of neuropathy with doses as low as 200 mg per day. [150,151]

Prior to the addition of carbidopa to L-dopa treatment for PD, it was frequently noted that pyridoxine supplementation resulted in a loss of the L-dopa effect, with an increase in Parkinsonian symptoms.[154-159] This effect is due to inhibition of peripheral decarboxylation of L-dopa.[160] However, use of peripheral decarboxylase inhibitors such as carbidopa with L-dopa blocks the drug interaction, such that the efficacy of the two drugs is unaffected by pyridoxine.[158-160]

We found no safety concerns related to cobalamin, either in oral or parenteral form.

A systematic review of the safety of folic acid supplements was performed by Campbell in 1996, prior to the policy of mandatory grain fortification in the US.[161] Several potential safety issues were discussed including masking of thiamine deficiency, neurotoxicity, drug antagonism, reduced zinc absorption, and hypersensitivity. Folate repletion in B12 deficient individuals is well-known to post the anemic manifestations of pernicious anemia while allowing posterolateral spinal cord degeneration to progress. This effect is generally seen only with higher doses of folate (≥5 mg daily) and can be avoided by testing for B12 deficiency.[161,162] The question of neurotoxicity has been tested in patients with PD as described above (McGeer 1972). Several case reports of increased frequency of seizures in epileptics have been reported with folate doses of 5 to 30 mg;[162] although this possible effect may in part be due to interactions between folate and anti-convulsant drugs due to their effect on folate metabolism.[161] However, no drugs used specifically for neurodegenerative disorders interfere with folate metabolism. Campbell also found a limited number of case reports describing hypersensitivity reactions to oral and parenteral folic acid, but concluded that the reactions were probably to contaminants in the folate formulations.

Table 38. Institute of Medicine Dietary Reference Intakes of B vitamins and adverse effects

Nutrient	Life Stage Group	RDA	UL[a]	Adverse effects of excessive consumption
Thiamine	**Males**	(mg/d)		No adverse effects from food or supplements have been reported. Because data on the adverse effects of thiamin are limited, caution may be warranted.
	≥31 yr	1.2	ND	
	Females			
	≥31 yr	1.1	ND	
Riboflavin	**Males**	(mg/d)		No adverse effects from food or supplements have been reported. Because data on the adverse effects of riboflavin are limited, caution may be warranted.
	≥31 yr	1.3	ND	
	Females		ND	
	≥31 yr	1.1	ND	
Vitamin B6	**Males**	(mg/d)		No adverse effects from food or supplements have been reported. Because data on the adverse effects of B6 are limited, caution may be warranted. Sensory neuropathy has occurred from high intakes of supplemental forms.
Comprises a group of 3 vitamers: pyridoxal, pyridoxine, pyridoxamine; and 5'-phosphate coenzymes of each vitamer	31-50 yr	1.3	100	
	≥50 yr	1.7	100	
	Females			
	31-50 yr	1.3	100	
	≥50 yr	1.5	100	
Vitamin B12	**Males**	(µg/d)		No adverse effects from food or supplements have been reported. Because data on the adverse effects of B12 are limited, caution may be warranted.
Including its coenzymes methylcobalamin and adenosylcobalamin	≥31 yr	2.4	ND	
	Females			
	≥31 yr	2.4	ND	
Folate	**Males**	(µg/d)		Masks neurological complication in people with vitamin B12 deficiency. No adverse effects from food or supplements have been reported. Because data on the adverse effects of folate are limited, caution may be warranted. The UL for folate applies to synthetic forms obtained from supplements and/or fortified foods.
Note: Given as dietary folate equivalents (DFE). 1 DFE = 1 µg food folate = 0.6 µg of folic acid from fortified food or as a supplement consumed with food.	≥31 yr	400	1000	
	Females			
	≥31 yr	400	1000	

Derived from Institute of Medicine report accessed at www.iom.edu/Object.File/Master/7/296/0.pdf via www.nal.usda.gov/fnic/etext/000105.html (accessed July 27, 2005).
RDA = Recommended Daily Allowance; UL = Upper Limit.

[a] UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for thiamin, riboflavin, or vitamin B12. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

Berries

In this section, we summarize the results from human and animal or in vitro studies of berries and/or the constituents in berries in relation to age-related neurodegenerative disorders. The four Key Questions to be answered are as follows:

1. What are the constituents in berries with beneficial nerve- and brain-related health effects (from in vitro, animal, and human studies)?
    a. In what other food sources are these constituents found?

2. What is the evidence regarding mechanisms of action of berry constituents for preventing, decreasing the rate of progression of, or reversing the neurological changes associated with age-related neurodegenerative conditions, including Parkinson's or Alzheimer's disease?

3. What is the evidence that the constituents of berries can prevent, decrease the rate of progression of, or reverse the neurological changes associated with age-related neurodegenerative conditions, including Parkinson's or Alzheimer's disease in humans
    a. Is the source, species, dose, composition, characteristics, or processing of berries and berry constituents related to the effect of the intervention?

4. What adverse events in humans have been reported in the literature for the constituents in berries?
    a. Do the frequency of adverse events vary with source, dose, or other evaluated factors?

Findings are presented in the order of the Key Questions.

Searches of the MEDLINE® and CAB Abstracts™ databases for human, animal, and in vitro studies yielded 4,633 citations. After screening of the titles and abstracts, 151 articles were retrieved for examination. We retrieved an additional 20 articles identified from review articles, study reference lists, and domain experts. One human study and 18 animal or in vitro studies (with 19 experiments) were included in this review. Of note, 16 (89%) of these studies have been conducted by a single group of investigators at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University both with and without the cooperation of other research centers.

Qualifying studies are presented in summary tables in the appropriate sections. Details regarding all included studies are available in the evidence tables*

Constituents in Berries

Berries are generally high in fiber and some species may be high in vitamin C. Folate is the major B vitamin in some berries, although it does not contribute a substantial amount to a typical

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/berry/berry.pdf.

diet compared to other food items (Table 39). Complete nutrient contents of berries can be found in the USDA National Nutrient Database for Standard Reference (www.nal.usda.gov/fnic/foodcomp/search/). Like other fruits or vegetables, berries also contain various phytochemicals or phytonutrients, which might have antioxidant or anti-inflammatory effects. Flavonoids are believed to be the main antioxidants in berries. The flavonoid contents of various berries can be accessed in the USDA database for the "Flavonoid Contents of Selected Foods."[163] Currently, there is no standard nutrient database for other phytochemicals in fruit and vegetables. Research has derived some composition data on the anthocyanins and phenolics contents in diverse small fruits, including berries.[164,165] Of the three included studies that evaluate the effects of the constituents in berries, only a limited number of the numerous constituents in berries have been examined. These included tannins (procyanidin and prodelphinidin), anthocyanin and phenolics, from various berries.

Table 39. USDA nutritional facts on selected raw berries (1 cup) [a]

Fresh fruit	Weight	Fat	Protein	Fiber	Sugar	Vitamin A	Vitamin C	Potassium	Thiamine	Riboflavin	Vitamin B6	Folate
Blackberries	144 g	1 g	2 g	8 g	7 g	308 IU	30 mg	233 mg	0.03 mg	0.04 mg	0.04 mg	36 µg
Blueberries	145 g	0 g	1 g	4 g	14 g	78 IU	14 mg	112 mg	0.05 mg	0.06 mg	0.08 mg	9 µg
Strawberries	147 g	0 g	1 g	3 g	7 g	18 IU	86 mg	225 mg	0.04 mg	0.03 mg	0.07 mg	35 µg

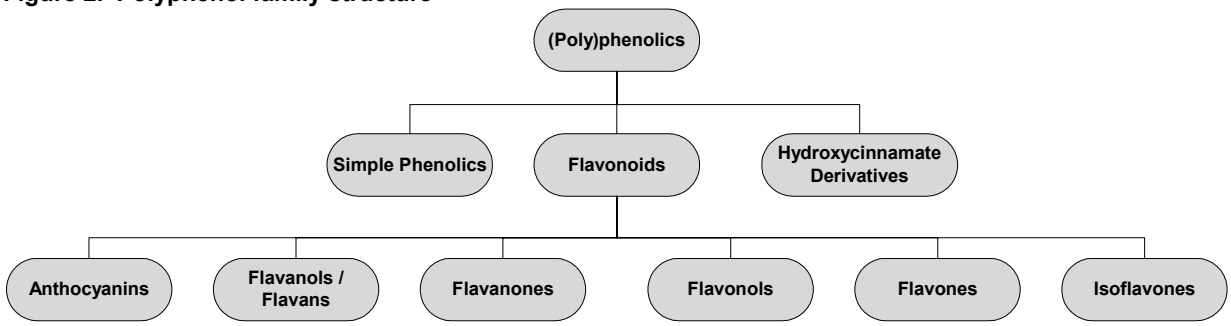
[a] Nutrient data were obtained from the USDA Nutrient Database for Standard Reference (www.nal.usda.gov/fnic/foodcomp/search/)

Antioxidants in Berries

Antioxidants have protective effects against free radicals, highly reactive substances that result from normal metabolism and from exposure to environmental factors like cigarette smoke and ultraviolet light. Free radicals cause cellular damage by attacking the body's cell membranes, proteins, and DNA. Berries, such as blueberries, blackberries, cranberries, black raspberries, raspberries, and strawberries, have higher total antioxidant capacity than other fruits or vegetables, according to the commonly used oxygen radical absorbance capacity (ORAC) and ferric-reducing ability of plasma (FRAP) assays.[164,166-168] The ORAC assay is based on an antioxidant's ability to react with or neutralize free radicals generated in the assay systems. The FRAP assay measures the reduction of ferric iron (Fe^{3+}, oxidized form) to ferrous iron (Fe^{2+}, reduced form) in the presence of antioxidants.[167]

Flavonoids are members of the polyphenol family, important phytochemicals derived from plants and having a combination of anti-oxidative, anti-viral, and anti-carcinogenic properties (Figure 2). Although the predominant flavonoid depends on variety and species, flavonoids are found mostly in celery, cranberries, onions, kale, dark chocolate, broccoli, apples, cherries, berries, tea, red wine, purple grape juice, parsley, soybeans, tomatoes, eggplant, and thyme.[163] Anthocyanins and/or proanthocyanidins (a class of flavonoid compounds) are the main antioxidants compounds found in berries, and they might have anti-inflammatory effects.

Figure 2. Polyphenol family structure



EXAMPLES:

Anthocyanins:	cyanidin, malvidin, petunidin etc. (all have sugars attached)
Flavanols / Flavans:	catechin, epicatechin, proanthocyanidins
Flavanones:	hesperetin, naringenin, eriodictyol
Flavonols:	quercetin, myricetin, kaempferol (most have sugars attached)
Flavones:	apigenin, luteolin
Isoflavones:	daidzein, genistein, glycitein
Hydroxycinnamates:	chlorogenic acid
Simple Phenolics:	phloridzin

Animal and In Vitro Studies: Mechanisms of Action

All studies related to mechanisms of action of berry constituents (or whole berries) have been performed in animal or in vitro models. Among 18 animal or in vitro studies (with 19 experiments) investigating berries and neurocognitive function or processes, four studies[169-172] examined the effects of specific berry constituents on animal performance in neurocognitive testing or on their brain biochemistry. The remaining 14 studies (with 15 experiments)[173-186] used berry extracts that supplemented normal diet or were added to in vitro media.

Effects of the Constituents in Berries

Study Descriptions. Four studies, two of high quality and two of moderate quality, were included in this section. [169-172] Of the four studies, only a limited number of the numerous constituents in berries have been examined. These include tannins, anthocyanin and phenolics, from various berries (Table 40). Each study examined the effects of different berry constituents.

Overall Effects. Saija 1990 found that injecting 200 mg/kg bilberry anthocyanin extracts intraperitoneally in adult rats for 3 days significantly increased rats' brain uptake of triiodothyronine (T3).[169] The findings generated the hypothesis that the berry anthocyanins might cross the BBB and block the 5'-deiodinase activity and, therefore, the intracerebral formation of T3 from T4, thereby simultaneously stimulating T3 transport into the brain.

Wang 1996 measured the concentrations of tannins from 18 plant sources that were required for 50 percent inhibition (IC_{50} values) of brain protein kinase C (PKC). Wang found that blueberry, red currant, and gooseberry tannins have similar IC_{50} values as other plant tannins. Additionally, the IC_{50} values of these three tannins were not significantly different from each

other. No measurements were made regarding possible effects of PKC inhibition.[171] PKC is known to be involved in eukaryote cell signal transduction.

Andres-Lacueva 2005 assessed whether anthocyanins might be found in brain areas associated with cognitive performance following blueberry supplementation in old rats, and the effects of the blueberry supplementation in rats' diet on the performance of Morris Water Maze. The rats' standard diet was augmented with either blueberry extracts or dried corn, which replaced 2 percent of the diet. They found that following 10 weeks of dietary supplementation with 2 percent of blueberry extracts, anthocyanins were found in the brains of all rats fed the blueberry diet, while no anthocyanins were detected in the brains of rats fed the corn diet. There was no difference in Morris Water Maze escape latency learning over days between blueberry- and corn-fed rats. However, among blueberry-fed rats, there was a significant negative correlation between day 4 re-learning (mean latency for trials 2-6) and number of total anthocyanins measured in the cortex (r=-0.78, *P*=0.02); i.e., as anthocyanin number increased, the latency to find the platform decreased. Also as anthocyanin number increased, there was a trend for the rat to spend more time searching in the location of the previous platform location on the probe trial (r=0.91, *P*=0.09).

Shukitt-Hale 2005 is the only study that compared the effects of specific berry constituents on neurocognitive outcomes. They examined aged rats' performance in neurocognitive testing, along with possible mechanisms of action regarding brain biochemical changes. The rats' standard diet was augmented with each of four berry extracts, which replaced 2 percent of the diet. The total phenolics in these four berry extracts were similar, while black currant or boysenberry extracts had higher amount of anthocyanin than blueberry or cranberry extracts. They tested whether the loss of the ability of cells to increase the biomarker heat shock protein (HSP70), as a means to respond to insults such as ischemia, inflammatory agents and reactive oxygen species, may contribute to the age-related declines in both neuronal and behavioral functioning. In addition, striatal dopamine release was assessed because it is believed to be a sensitive marker for assessing striatal muscarinic sensitivity in aging.

Blueberry and cranberry extracts, but not black currant and boysenberry extracts, had a significant beneficial effect on performance by the rats on the inclined screen test, one of five psychomotor functions tested. The cranberry extract group (that had improved function) and the black currant extract group (that did not have improved function) had significantly increased striatal dopamine release compared to the control and boysenberry extract groups; the blueberry extract group was not examined for dopamine release.

HSP70 responsiveness in the blueberry extract group was significantly higher than the control group and the cranberry extract group showed a trend toward higher HSP70 responsiveness than the control group, while the black currant and boysenberry extract groups did not show such responsiveness. Furthermore, rats' neurocognitive performance, as measured by latency to fall from the inclined screen, was positively related to the percent change in HSP70 (r=0.39, *P*=0.05).

The inclined screen, dopamine release and HSP70 results all suggested that there is a range of effectiveness associated with the different berry extracts. However, it does not appear that the anthocyanin component is solely responsible for these improvements, as the black currant and boysenberry extracts are higher in anthocyanin level, but not as effective in improving motor performance. Of note, there was no significant effect on rats' performance in the Morris Water Maze among the four berry extract groups when compared to control. This test is among the more standardized and validated tests of neurocognitive and behavioral function in rodents.[187]

Summary. Of the four included studies, only a limited number of the numerous constituents in berries have been examined. Each study examined the effects of different berry constituents. One study showed that injecting 200 mg per kg bilberry anthocyanin extracts intraperitoneally in adult rats for 3 days significantly increased rat's brain uptake of T3. Another study measured the IC_{50} of brain PKC for 18 plant tannins in an in vitro study. Blueberry, red currant, and gooseberry tannins have similar IC_{50} values as other plant tannins. Additionally, the IC_{50} values of these three tannins were not significantly different from each other. However, the biological significance of this in vitro study in live animals is unknown. Only the most recent studies evaluated the effects of specific berry constituents on neurocognitive outcomes. Two studies examined aged rats' performance in neurocognitive testing: both found no difference in the learning performances; one found improvements in motor performances. Of these, one study also demonstrated that the anthocyanins in blueberry extracts were able to cross the BBB and the number of the total anthocyanins measured in the brain is associated with rats' learning performance. Another study examined the possible mechanisms of action regarding brain biochemical changes to rats' performance in neurocognitive testing. The results suggested that there is a range of effectiveness associated with the different berry extracts as shown in the results from rats' performance in the inclined screen test, dopamine release and heat shock protein. However, it does not appear that the anthocyanin component of the berry extracts is solely responsible for these improvements, as the black currant and boysenberry extracts are higher in anthocyanin level, but not as effective in improving motor performance.

Table 40. Effects of constituents in berries on animal's performance in neurocognitive testing or on their brain biochemistry

Study, Year	Model Age/Weight		Duration	Intervention			N	Control	N	Neurocognitive Test	Group	Results	*P*	Biochemical Measures	Group	Results	*P*	Quality
Saija, 1990	Rats	S-D 300-350 g	3 days	Bilberry anthocyanins [a]		200 mg/kg i.p.	nd	Vehicle	nd					Brain uptake of T3		+	<.05 [b]	B
Wang, 1996	Rat brain	PKC [c]		Blueberry tannins [d]				(Other tannins)						Brain PKC inhibition		0 [e]	NS btw tannins	A
				Red currant tannins [f]												0 [e]		
				Gooseberry tannins [g]												0 [e]		
Andres-Lacueva, 2005	Rat, male	F344 19 mo	7-10 wk	Blueberry extracts		2% of diet	8/4 [h]	NIH-31 w/ 2% dried corn	8/4	MWM- time to reach platform		0		Anthocyanin profile distribution in brain regions (cerebellum, cortex, striatum; hippocampus)		+	nd	A
										MWM- time searching		0						
Shukitt-Hale, 2005	Rat, male	F344 19 mo	13-16 wk	BB	An: 1.3	Ph: 1.2	nd	NIH-31	nd	Rod Walk	All	0		Dopamine release	BB	nd		B
				BC	An: 8.7	Ph: 2.9	nd			Wire Suspension	All	0			BC	+	.004	
				BS	An: 9.2	Ph: 2.0	nd			Plank Walk	All	0			BS	0		
				CB	An: 3.3	Ph: 3.6	nd			Inclined Screen	BB	+	.04		CB	+	.007	
											BC	0		Hippocampal HSP70	BB	+	.001	
											BS	0			BC	0		
											CB	+	.001		BS	0		
										Accelerating Rotarod	All	0			CB	~+	.06	
										Morris Water Maze	All	0						

An = anthocyanin (mg/g extracts), BB = blueberry extracts, BC = black currant extracts, BS = boysenberry extracts, btw = between, CB = cranberry extracts, F344 = Fischer 344, HSP70 = heat shock protein 70, i.p. = intra-peritoneal, N/A = not applicable, nd = no data or not done, NS = not statistically significant, Ph = total phenolics (mg/g extracts), PKC = protein kinase C, S-D = Sprague-Dawley, T3 = triiodothyronine, MWM = Morris Water Maze.

+ Berry-fed animals performed better than non-berry-fed animals
0 No difference in performance
– Berry-fed animals performed worse than non-berry-fed animals

[a] Extract containing up to15 anthocyanins.
[b] A significant increase in T3 transport into frontal cortex, temporoparietal cortex, occipital cortex, hippocampus, thalamus, hypothalamus and brain-stem, but no significant change in T3 transport into striatum, inferior colliculus, and cerebellum.
[c] Study measured the concentrations of 18 plant tannins required for 50% inhibition (IC50 values) of brain PKC.
[d] Containing 77% procyanidin and 23% prodelphinidin.
[e] Compared to non-berry tannins.
[f] Containing 78% procyanidin and 22% prodelphinidin.
[g] Containing 96% procyanidin and 4% prodelphinidin.
[h] 8 animals per group for neurocognitive test between 7 and 8 weeks after receiving the diets; brains from 4 animals per group were harvested for brain biochemical measures after 10 weeks of diets.

Effects of Berry Extract Supplementation

Berry extracts were used to supplement animals' diet or added to in vitro study media in 14 studies with 15 experiments that examined animal's performance in neurocognitive testing or brain biochemistry or histology.[173-186] Of these, two studies used specific animal or in vitro models of AD. The remaining 13 studies used adult or aged rat models. All of these studies (including the rat neurocognitive function study described above) are from the same group of investigators.

Study Descriptions. Only limited types of berry extracts were examined across the 14 studies with 15 experiments (Table 41). Blueberry extracts were used in 11 studies, of which only one study specified the species of blueberries (i.e., "wild" vs. "tif-blue" blueberries, a variety of rabbiteye blueberry).[186] Strawberry extracts were used in 11 studies, none of which reported the species. Seven of these studies used both blueberry and strawberry extracts, including one study that used five different berry extracts, including blueberry, strawberry, black currant, boysenberry, and cranberry extracts.[181] All berry extracts were freeze-dried and aqueous extracted, prepared by homogenizing, centrifuging, and then freeze drying. All 13 studies that used adult or aged rat models were based on a single central hypothesis, namely that the increase in dietary antioxidant levels (by supplementation with berry extracts) might decrease the aging-induced oxidative stress (and/or various physiological changes due to the increased oxidative stress) thus reversing the age-related neurodegenerative deficits. However, the studies did not elaborate on which "antioxidants" in these berry extracts might be responsible for the effects. With a similar central hypothesis, the two studies of animal or in vitro models of AD further examined the effects of berry extracts on fibrillar amyloid β deposits in mice's brain and on Ca^{2+} recovery following amyloid β treatment in vitro.[180,181] Most studies are of high quality. Studies that were downgraded to moderate or poor quality were due to poor reporting, no repeated measures, or lack of neurocognitive function measures.

Overall Effect

Blueberry extract supplementation. The effects of blueberry supplementation on animal's performance in neurocognitive testing or brain biochemistry or histology in adult or aged rat models are summarized in Figure 3. In these nine studies, blueberry extract supplementation showed positive or protective effects on all biochemical markers and histology findings examined in rats' brain, although only some of the neurocognitive tests and psychomotor functions were significantly improved in blueberry-extract-fed rats. Only one study correlated the biochemical markers changes in rats' brain with rats' performances in cognitive function tests.[175] Nineteen-month-old male F344 rats were fed either the control diet or the blueberry-extract diet for 8 weeks before they were tested for Radial Arm Water Maze (RAWM) performances. The blueberry-extract diet equaled 2 percent of the control diet supplemented with blueberry extracts, which was approximately equivalent to the consumption of 4 g of blueberry extract per day. RAWM performance was tested for five consecutive days. Repeated measure analysis across days revealed a significant day effect for latency ($P<0.0001$), suggesting that rats in both groups could successfully learn the task on days 1 to 3. The lack of interaction between groups suggested that the rate of learning on days 1 to 3 did not differ across groups. On day 4, compared to animals fed the control diet, blueberry-extract-fed rats had significantly fewer reference memory errors ($P<0.05$) and total memory errors ($P<0.05$), and also showed a trend

towards fewer working memory errors (P<0.06). However, there was no significant difference in RAWM performances seen between the two groups on day 5. It was also found that the blueberry extract supplementation significantly increased hippocampus insulin growth factor-1 (IGF-1), IGF-1R, and extracellular-signal-regulated-kinase (ERK) activation. These changes of brain biomarkers were significantly associated with the decreases in total memory errors and reference memory errors but not working memory errors on day 4. In addition, blueberry extract supplementation significantly increased proliferation of precursor cells in the dentate gyrus (or neurogenesis) and the neurogenesis was significantly associated with the improvements in RAWM tests. Finally, in order to see if neurogenesis, growth factors, and ERK, in combination or synergistically, were associated with the improvements in RAWM tests in aged blueberry-extract-supplemented rats, the associations between these brain biomarkers were examined. A statistically significant positive correlation between ERK activation and IGF-1 and IGF-1R levels was found (r=0.75, P<0.05), while the increased IGF-1 and IGF-1R levels, and ERK activation were not associated with neurogenesis.

Strawberry extract supplementation. The effects of strawberry supplementation on animal's performance in neurocognitive testing or brain biochemistry or histology in adult or aged rat models are summarized in Figure 4. Nine of 10 studies showed positive or protective effects of strawberry-extract supplementation on all of the biochemical markers examined in rats' brain, although only some of the neurocognitive tests and psychomotor functions were significantly improved in strawberry-extract-fed rats. No study correlated the biochemical markers changes in rats' brain with rats' performances in neurocognitive function tests.

Alzheimer's disease models. One animal study[180] and in vitro study[181] used models of AD to examine the effects of berry extracts.

In the animal study, mice transgenic for amyloid precursor protein (APP) and presenilin-1 (PS1) mutations were used to model human AD.[180] These mice are prone to fibrillar amyloid β deposits in cerebral cortex and hippocampus early in the life-span with later changes in cognitive behavior. Four-month-old transgenic and wild type mice were fed either the control diet or the blueberry-extract diet for 12 weeks before they were tested for Y maze performances. The blueberry-extract diet was 2 percent of the control diet supplemented with blueberry extracts, which was approximately equivalent to the consumption of 4 g of blueberry extract per day. Blueberry extract supplementation had a beneficial effect on Y-maze performance in transgenic mice but not in wild type mice. In the transgenic mice, there was no significant change in brain amyloid β deposits or calcium-dependent phospho-protein kinase Cα (PKCα), while a significant increase in brain neutral sphingomyelin-specific phospholipase C (N-Sase), low Km guanosine triphosphase (GTPase), ERK, and protein kinase Cγ (PKCγ) activities was found. Furthermore, the correlation between these brain biomarkers and the Y maze performances by the mice was examined. A positive correlation between GTPase activity and Y-maze alternation was found in the striatum but not in the hippocampus or cortex. A negative correlation between N-Sase activity and Y-maze alternation was found in the striatum but not in the hippocampus or cortex. The correlation between all other brain biomarkers and Y-maze alternation did not reach statistical significance.

In the in vitro study, COS-7 cells (ATCC) transfected with rat muscarinic receptor subtype 1 or 3 DNA (M1AchR) were used.[181] Five different berry extracts (2 mg per mL blueberry, 2 mg per mL black currant, 2 mg per mL boysenberry, 0.5 mg per mL strawberry, or 1 mg per mL cranberry extracts) were dissolved in growth media and M1AchR-transfected COS-7 cells were

subsequently incubated with the treated growth medium. Following these incubations the cells were washed with extract-free growth medium prior to testing. Ca^{2+} Recovery following 0 or 1 mM dopamine or 0 or 100 μM amyloid β treatment was tested. Recovery was determined by assessing the time (within 300 sec) for the Ca^{2+} level to return to 20 percent of the increase following depolarization in the cells that responded. In the absence of pre-treatment (control condition) there were significant effects of both dopamine and amyloid β on recovery of the M1-transfected cells (e.g., control vs. dopamine- or amyloid β-treated cells with no extract pre-treatment, $P<0.001$) and all berry extract pre-treatments did not show any significant effect on Ca^{2+} recovery. However, all five berry extract pre-treatments significantly reduced the deleterious effects of dopamine, and blueberry, black currant, boysenberry and cranberry but not strawberry, extract pre-treatments significantly reduced the putative toxic effects of amyloid β.

Summary. Only strawberry and blueberry extracts were used to examine the effects of extract supplementation on animal performance in neurocognitive testing or brain biochemistry or histology using a normal-aging rat model. The mechanism of actions tested were similar for both berry extracts although only one study, using blueberry extract, examined the direct relationship between the changes in brain biomarkers and the performance in neurocognitive function tests. Blueberry and strawberry extract supplementation showed positive or protective effects on almost all biochemical markers and histology findings examined in rats' brain, although only some of the neurocognitive tests and psychomotor functions were significantly improved in these berry-extract-fed rats.

Only two studies used models of AD to examine the effects of various berry extracts. The results suggested that it may be possible to reduce both the deleterious effects of dopamine and the putative toxic effects of amyloid β via various berry extracts as shown in the in vitro study. Results from the animal study that used mice transgenic for APP and PS1 mutations to model human AD showed that the blueberry extract supplementation seemed to have prevented the deficits in Y-maze performance seen in the transgenic animals fed the control diets, although it did not affect amyloid β deposits.

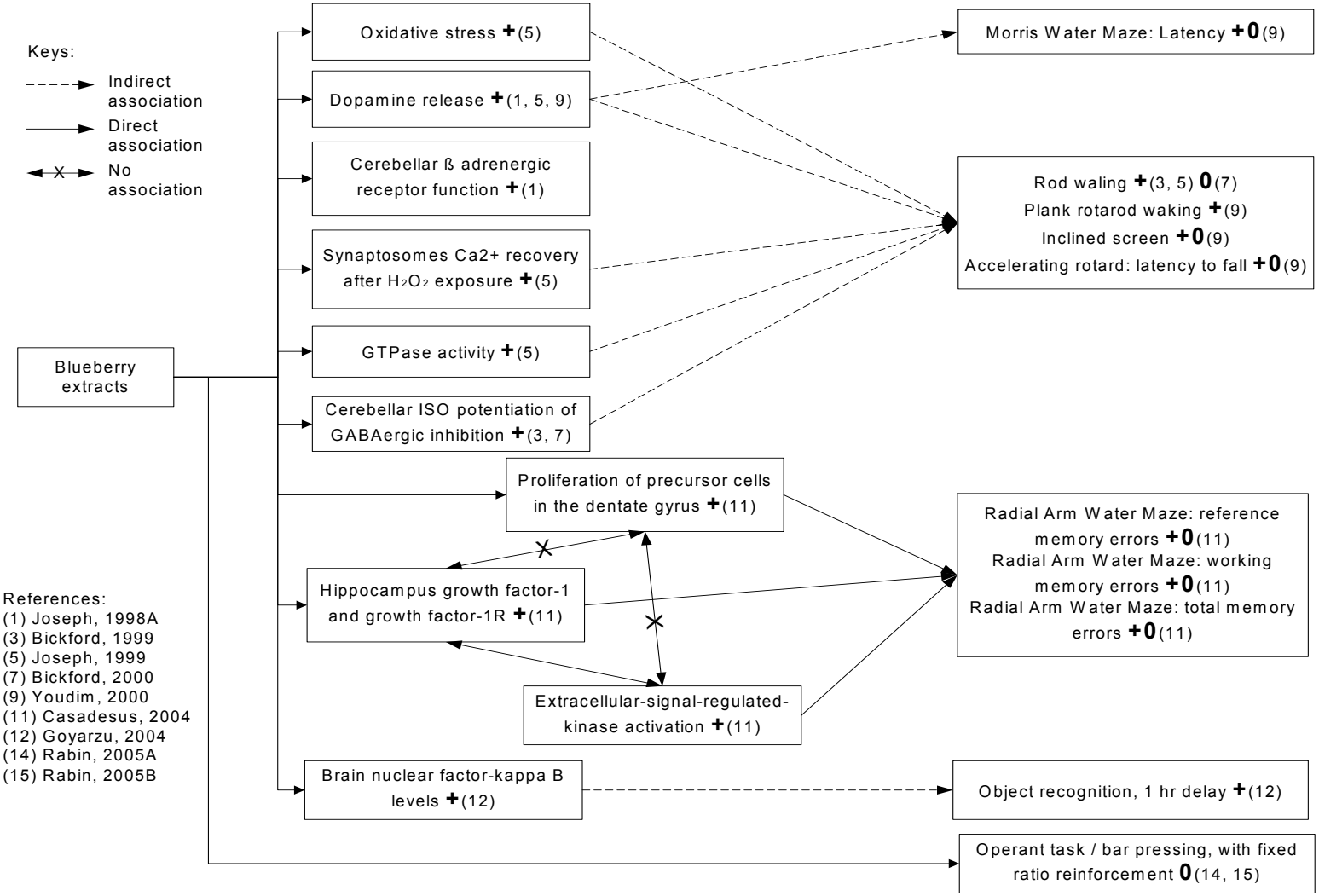


Figure 3. Summary of the effects of blueberry extract supplementation on animal's performance in neurocognitive testing or brain biochemistry or histology in adult or aged rat models

+ Berry-fed animals performed better than non-berry-fed animals
0 No difference in performance
– Berry-fed animals performed worse than non-berry-fed animals

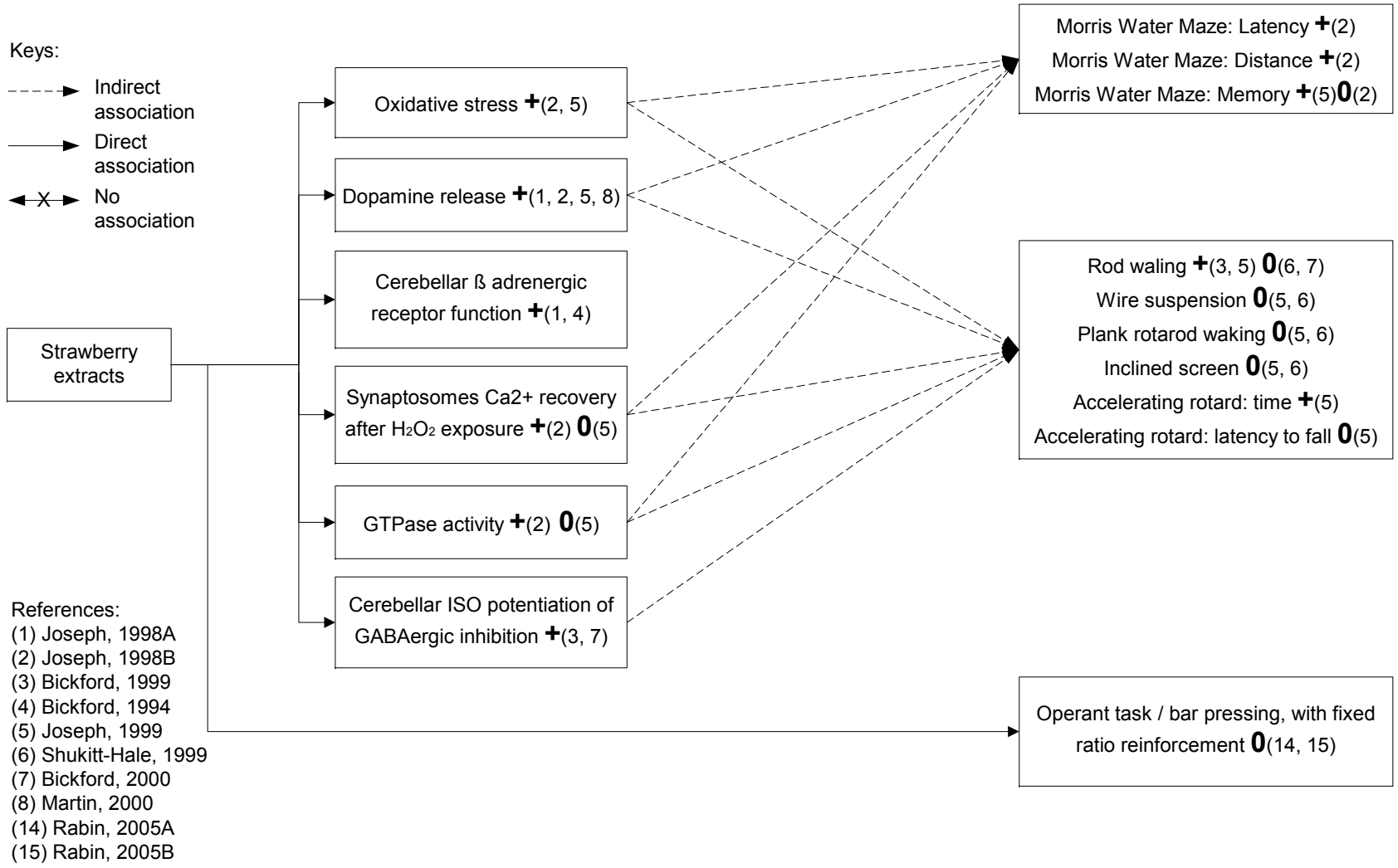


Figure 4. Summary of the effects of strawberry extract supplementation on animal's performance in neurocognitive testing or brain biochemistry or histology in adult or aged rat models

+ Berry-fed animals performed better than non-berry-fed animals
0 No difference in performance
– Berry-fed animals performed worse than non-berry-fed animals

Table 41. Effects of berry extracts on animal performance on neurocognitive testing or brain biochemistry or histology

Study, Year	Model	Age/Weight	Duration (mo)	Intervention		N	Control	N	Neurocognitive Test	Group	Results	*P*	Biochemical / Histology Measure	Group	Results	*P*	Quality
Normal aging model																	
Joseph, 1998A	Rats	F344, 6-8 mo	2	Blueberry extracts	10 g/kg	nd	AIN-93	nd					Dopamine release[e]	B	+	nd	C
														S	+	nd	
				Strawberry extracts	9.4 g/kg	nd							Cerebellar ß adrenergic receptor function	B	+	<.01	
														S	+	<.01	
Joseph, 1998B	Rats, male	Fischer, 6 mo	8	Strawberry extracts	9.5 g/kg	8[a]	Modified AIN-93	8[a]	MWM: Latency		+	<.05	Dopamine release (striatal)		+	<.03	A
									MWM: Distance		+	<.01	Ca^{2+} recovery after H_2O_2 exposure (synaptosomes)		+	<.02	
									MWM: Memory		0		Oxidative stress (cerebellar)		+	<.0001	
													GTPase activity (striatal)		+	<.0001	
Bickford, 1999	Rats	F344, 6 mo	2	Blueberry extracts	10 g/kg	nd	AIN-93		Rod walking[e]	B	+	nd	Cerebellar ISO potentiation of GABAergic inhibition[e]	B	+	nd	C
				Strawberry extracts	9.4 g/kg	nd				S	+	nd		S	+	nd	
Bickford, 1999	Rats	F344, 6 mo	9	Strawberry extracts	9.4 g/kg	nd	AIN-93						Cerebellar ß adrenergic receptor function		+	<.01	C
Joseph, 1999	Rats	F344, 19 mo	2	Blueberry extracts	10 g/kg	10	Modified AIN-93	10	Rod walking time	B	+	<.05	Dopamine release (striatal)	B	+	<.0001	A
										S	+	<.05		S	+	<.0001	
				Strawberry extracts	9.4 g/kg	10			Rod walking (latency to fall)	B	+	<.01	GTPase activity (striatal)	B	+	<.001	
										S	+	<.01		S	0		
									Wire suspension	B	0		Ca recovery after H_2O_2 exposure (synaptosomes)	B	+	<.05	
										S	0			S	0		
									Plank walking	B	0		Oxidative stress (striatal)	B	+	<.005	
										S	0			S	+	<.002	
									Inclined screen	B	0						
										S	0						
									Accelerating rotarod time	B	+	<.05					
										S	+	<.05					
									Accelerating rotarod (latency to fall)	B	~+	.06					
										S	0						
									MWM: Memory (learning trial 1→2)	B	+	<.01					
										S	+	<.05					

Continued

Table 41. Effects of berry extracts on animal performance on neurocognitive testing or brain biochemistry or histology (continued)

Study, Year	Model Age/Weight		Duration (mo)	Intervention		N	Control	N	Neurocognitive Test	Group	Results	*P*	Biochemical / Histology Measure	Results	*P*	Quality
Shukitt-Hale, 1999	Rats	C57BL.6NIA, 18 mo	6	Strawberry extracts	1% of diet	10	Modified AIN76	8	Rod walking		**0**					A
									Wire suspension/wire hanging		**0**					
									Plank walking		**0**					
									Inclined screen		**0**					
Bickford, 2000	Rats, male	F344, 18 mo	2	Blueberry extracts	18.6 g/kg	8	Modified AIN-93	14	Rod walking asymptote (time improvement)	B	**0**		Cerebellar ISO potentiation of GABAergic inhibition	B	**+**	<.001	A
										S	**0**			S	**+**	<.05
				Strawberry extracts	14.8 g/kg	8			Rod walking slope (rate of learning)	B	**0**					
										S	**0**					
Martin, 2000	Rats, male	F344, 15 mo	8	Strawberry extracts	9.5 g/kg	20	Modified AIN-93	20					Dopamine release (striatal)		**+**	<.05	B
Youdim, 2000	Rats, male	F344, 17 mo	2	Blueberry extracts, "wild"	2% of diet	14	Modified NIH-31[b]	12	Accelerating rotarod (latency to fall)	Bw	**+**	<.05	Dopamine release (striatal)	Bw	**+**	<.05	A
										Bt	**0**			Bt	**+**	<.05
									Inclined screen (latency to fall)	Bw	**0**					
										Bt	**~+**	.06				
				Blueberry extracts, "tif-blue"	2% of diet	13			Plank walking (latency to fall)	Bw	**+**	<.05				
										Bt	**+**	<.05				
									MWM (latency to find platform) – trial 1	Bw	**0**					
										Bt	**+**	<.05				
									MWM (latency to find platform) – trial 2	Bw	**0**					
										Bt	**0**					
Casadesus, 2004	Rats, male	F344, 19 mo	2	Blueberry extracts	2% of diet	5	NIH-31	5	Reference memory errors	Day 1-3	**0**		Proliferation of precursor cells in the dentate gyrus		**+**	<.05	A
										Day 4	**+**	<.05				
										Day 5	**0**					
									Working memory errors	Day 1-3	**0**		Hippocampus growth factor-1 (IGF-1)		**+**	<.001	
										Day 4	**+**	<.06				
										Day 5	**0**					
									Total memory errors	Day 1-3	**0**		Hippocampus growth factor-1R (IGF-1R)		**+**	<.005	
										Day 4	**+**	<.05				
										Day 5	**0**					
													Extracellular-signal-regulated-kinase (ERK) activation		**+**	<.01	

Continued

Table 41. Effects of berry extracts on animal performance on neurocognitive testing or brain biochemistry or histology (continued)

Study, Year	Model Age/Weight		Duration (mo)	Intervention		N	Control	N	Neurocognitive Test	Group	Results	*P*	Biochemical / Histology Measure	Group	Results	*P*	Quality
Goyarzu, 2004	Rats, male	F344, 15 or 4 mo	4	Blueberry extracts	2% of diet	12	NIH-31, 15 mo	12	Object recognition, 1 hr delay	Aged Ctrl	+	<.01	Brain NF-κB levels[g]	Aged Ctrl	+[h]	<.03	A
							NIH-31, 4 mo	12		Young Ctrl	0			Young Ctrl	0[i]		
Rabin, 2005A	Rat, male	S-D 175-200 g	2[j]	Blueberry extracts	2% of diet	4	Modified NIH-31	8	Operant task / bar pressing, with fixed ratio reinforcement	6 mo pFe	0						A
										12 mo pFe	0						
				Strawberry extracts	2% of diet	4				6 mo pFe	0						
										12 mo pFe	0						
				Blueberry extracts + 1.5 Gy ^{56}Fe	2% of diet	8	Modified NIH-31 + ^{56}Fe	8		6 mo pFe	0						
										12 mo pFe	0						
				Strawberry extracts + 1.5 Gy ^{56}Fe	2% of diet	8				6 mo pFe	0						
										12 mo pFe	+	<.05					
Rabin, 2005B	Rat, male	S-D 175-200 g	2[j]	Blueberry extracts	2% of diet	4	Modified NIH-31	8	Operant task / bar pressing, with fixed ratio reinforcement	Age 9, 12 mo	0						A
										Age ?,?	0						
				Strawberry extracts	2% of diet	4				Age 9, 12 mo	0						
										Age ?,?	0						
				Blueberry extracts + 2.0 Gy ^{56}Fe	2% of diet	8	Modified NIH-31 + ^{56}Fe	8		Age 9, 12 mo	0						
										Age ?,?	0						
				Strawberry extracts + 2.0 Gy ^{56}Fe	2% of diet	8				Age 9, 12 mo	+	<.05					
										Age ?,?	0						

Continued

Table 41. Effects of berry extracts on animal performance on neurocognitive testing or brain biochemistry or histology (continued)

Study, Year	Model Age/Weight	Duration (mo)	Intervention	N	Control	N	Neurocognitive Test	Group	Results	*P*	Biochemical / Histology Measure	Group	Results	*P*	Quality
Alzheimer's disease model															
Joseph, 2003	Mice Transgenic[f], 4 mo	12	Blueberry extracts 2% of diet	3	Modified NIH-31	3	Y maze performance	Tg	+	<.05	Fibrillar Amyloid β deposits	Tg	0		A
								W	0			W	nd		
											N-Sase activity (striatal, hippocampal & cortex)[c]	Tg	+	<.01	
												W	+	<.01	
											Low Km GTPase activity (striatal)[c]	Tg	+	<.05	
	Mice Wild type, 4 mo			3		3						W	0		
											ERK activity (hippocampal)[d]	Tg	+	<.001	
												W	0		
											Phospho PKCα (hippocampal)[c]	Tg	+	<.05	
												W	0		
											PKCγ (striatal, hippocampal & cortex)[c,e]	Tg	0		
												W	0		
Joseph, 2004	COS-7 cells (ATCC) transfected with rat muscarinic receptor subtype 1 or 3 DNA		Blueberry extracts 2 mg/ml		No fruit extract pre-Rx						Ca^{2+} Recovery following 0 or 1 mM dopamine Rx	B	+	<.001	B
			Blackcurrant extracts 2 mg/ml									Bc	+	<.05	
			Boysenberry extracts 2 mg/ml									By	+	<.001	
			Strawberry extracts 0.5 mg/ml									S	+	<.01	
			Cranberry extracts 1.0 mg/ml									C	+	<.05	
											Ca^{2+} Recovery following 0 or 100 μM Aβ (25-35, 100 μM) Rx	B	+	<.05	
												Bc	+	<.05	
												By	+	<.05	
												S	0		
												C	+	<.05	

Aged Ctrl=when compared to the aged controls; Aβ= Rx=treatment; B=Blueberry extracts; Bc=Blackcurrant extracts; Bt=Blueberry extracts, tif-blue; Bw=Blueberry extracts, wild; By=Boysenberry extracts; C=Cranberry extracts; F344=Fischer 344; MWM=Morris water maze; nd=no data or not done; NF-κB=nuclear factor-kappa B; N-Sase=neutral sphingomyelin-specific phospholipase; pFe=after irradiation with ^{56}Fe; PKC=protein kinase C; S=Strawberry extracts; S-D=Sprague-Dawley; Young Ctrl=when compared to the young controls.

+ Berry-fed animals performed better than non-berry-fed animals
0 No difference in performance
– Berry-fed animals performed worse than non-berry-fed animals

[a] The number of animals per group was assumed from the total number of animals reported in the article.
[b] Information was inferred from subsequent publications. Control diet specification was, however, described in detailed as table format in the paper.
[c] 3 regions of brain were examined in this study, including striatal, hippocampus, and cortex. There was no significant effect was found in both groups if the brain region is not indicated in the parenthesis.

[d] Striatal and cortex regions were not examined for ERK activities
[e] Data not shown
[f] Transgenic for amyloid precursor protein (APP) and presenilin-1 (PS1) mutations; prone to fibrillar amyloid beta deposits in cerebral cortex and hippocampus and changes in cognitive behavior in later life
[g] Brain regions examined including frontal cortex, hippocampus, basal forebrain, stratum and cerebellum.
[h] In all regions except the basal forebrain, the difference was significant.
[i] In all regions except for the cerebellum, there was no significant difference between the aged rats fed blueberry-enrich diet and the young controls. In the cerebellum, the aged rats maintained on the blueberry-enriched diet had significantly higher NF-κB levels than young control. Notably, aged rats maintained on the control diet had significantly higher NF-κB levels than young rats maintained on the control diet in all regions except the striatum.
[j] Diet for 2 months; follow-up for 18 months.

Human Studies

Only one study examined the association between consumption of berries and age-related neurodegenerative disorders. In the late 1980s, Golbe et al. (1988) conducted a case-control study to examine the association between fruit and vegetable consumption in early life and the risk of PD among a group of non-vegetarian PD patients and their same-sex siblings The mean age of the participants at the time of survey was 62 years old.[188] Seventeen food items including fruit, vegetables, nuts, and salad oil or dressing were examined. Patients and same-sex siblings, in separate interviews, were each asked whether they or their spouse were more likely to eat each item between the time of marriage and age 40 years. Patients and siblings were first categorized by whether they consumed more, less, or the same amounts of different foods as their own spouses. Patient and sibling pairs (including spouses) were then categorized as concordant or discordant in their dietary habits (using an unverified, arbitrary decision process). Using discordant patient-sibling pairs, the odds ratio of PD was based on the patients who ate more of a food than their siblings compared to those who ate less. It was found that the preference to consume blueberries or strawberries was not statistically significantly associated with presence of PD. This study was deemed to be of poor quality due to measurement and recall biases, in addition to the unusual definitions for the consumption levels of fruit and vegetables, and the unverified categorization technique and statistical analysis.

We found no human interventional studies or clinical trials that met eligibility criteria and no correlational or observational study that evaluated AD.

Berry Adverse Events

The single human study of berry consumption was retrospective, therefore no study provided data regarding adverse events from berries in the setting of neurocognitive disorders. An electronic search (of MEDLINE® and CAB Abstracts™) for review and primary articles reporting on adverse events related to berries or berry constituents (not including allergic reactions or occupational exposures) identified two primary reports and a systematic review. This search captured only articles that were tagged for adverse events.

Canter and Ernst performed a systematic review of trials of bilberry-extracted anthocyanins for night vision.[189] They reported no adverse events in any of 12 eligible studies; although they did not clarify if adverse events were actually reported in these studies. They also reported in a post-marketing study of 2,295 participants, that 94 complained of side effects that were mainly gastrointestinal, or related to the skin or nervous system.[189,190]

An RCT of blackcurrant seed oil treatment for rheumatoid arthritis reported no dropouts due to adverse reactions.[191] One abstract of a case report described a man in his 70s, treated with digoxin, phenytoin, and warfarin, who had poor appetite and drank only cranberry juice post-chest infection.[192] After 6 weeks, the patient's international normalized ratio (INR) was greater than 50. The author noted that the Committee on Safety of Medicines has received seven other reports of possible interaction between warfarin and cranberry juice leading to changes in INR or bleeding.

Chapter 4. Discussion

Overview

Age-related neurocognitive disorders, primarily Alzheimer's disease (AD) and Parkinson's disease (PD), have a major impact on health and well-being among older Americans. The causes of the diseases are not yet well understood, including risk factors and associations with environmental factors. While some symptomatic treatments are available, no treatments are known to prevent, slow the progression of, or cure either AD or PD.

Separate lines of evidence have suggested that B vitamin status may be associated with risk and progression of AD and PD and that constituents of various berries may also effect progression of the diseases. This report summarizes the evidence for relationships between B vitamin status and supplementation, and separately berries, and age-related neurocognitive disorders. We summarize animal and in vitro evidence for specific putative mechanisms of actions and human studies of B vitamin supplementation or berries as treatments, of associations between dietary intake and disease, and associations between B vitamin status and disease.

We identified almost 7000 potentially relevant citations regarding B vitamins and almost 5000 potentially relevant citations regarding berries and neurocognitive disorders and function. Of these, we reviewed 85 human studies and 17 animal or in vitro studies of B vitamins and one human study and 18 animal or in vitro studies of berries. Among the human studies, the majority were cross-sectional studies that correlated B vitamin status with either cognitive function or dementia diagnosis. There were relatively few intervention studies, longitudinal dietary intake or B vitamin status association studies. The large majority of studies were of poor quality, with major deficits. The animal and in vitro studies primarily used otherwise healthy rats or mice on either vitamin-deficient or berry-supplemented diets; although several did use specific animal models for either AD or PD.

Both the human and the animal or in vitro studies were widely heterogeneous in doses used, measurement methods, definitions of dementia, cognitive function tests, and/or experimental design.

Main Findings

B Vitamins

This report includes evaluations of vitamins B1 (thiamine), B2 (riboflavin), B6 (pyridoxine and related compounds), B12 (cobalamin), and folate.

Mechanisms of Action. All studies were performed in animal or in vitro models. We specifically included studies of neurocognitive function, movement disorders, brain neurotransmitters, brain histopathology, expression or function of AD-related genes, and blood brain barrier (BBB) or cerebrovascular endothelial function. We excluded studies that used B vitamin antagonists.

In rat studies, thiamine depleted diets result in significantly damaged brain tissue with serious neurological pathology resulting in death. Thiamine deficiency also significantly impaired performances in several neurocognitive tests.

No study examined the effects of riboflavin (B2) on outcomes of interest.

No significant effects of B6 supplementation were found for rats learning or cognitive function, although there were some beneficial effects on motor function and behaviors. These effects, though, were not consistent across the studies and did not show a dose-response relationship.

One study showed that low dose (1 mg per kg diet) vitamin B12 supplementation alone had no significant effect on spontaneous movements and did not improve memory in rats with nucleus basalis magnocellularis lesions.

In normal animal models, there were no apparent pathologic changes in brain tissue after folate deprivation, although there was a degenerative appearance of the cerebrocortical microvascular wall. One study found that folate was protective against a sub-toxic dose of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which otherwise causes profound motor dysfunction similar to PD. Using the AD model of amyloid precursor protein (APP) mutant mice folate deficiency renders hippocampal CA3 neurons in APP mutant mice vulnerable to death by a mechanism that does not involve increased amyloid β-peptide production or deposition.

Only two studies examined the effects of B vitamins on the expression or function of AD-related genes. The series of animal experiments showed that while apolipoprotein E (ApoE)-deficient mice are less capable of buffering oxidative challenge in the central nervous system than are normal mice, the genetic deficiency could be alleviated with folate repletion. The results from the in vitro study demonstrated that presenilin-1 could be induced by folate and vitamin B12 deprivation. The other genes involved in APP processing and APP itself seemed to be independent of folate and vitamin B12 deprivation.

A study found that selective transport of pyruvate across the BBB was not functioning in a normal fashion in thiamine-deficient rats; BBB damage seen in later stages corresponded to damage seen from cold-injury edema and other models of cerebral edema. The leakage across the BBB appears to be predominantly through the mechanism of pinocytosis (introduction of fluids into a cell by invagination of the cell membrane, followed by formation of vesicles within the cells), not disruption of interendothelial junctions. Another study showed that folate is protective against homocysteine-induced cerebrovascular damage.

Overall, research has shown that there were negative effects of thiamine and folate deficiency or deprivation on animals' clinical status and/or histopathology, although not all deficient animals had worse performance in neurocognitive tests. Studies have found some positive effects of the supplementations of B6, B12, and folate on animal's performance in neurocognitive tests, but studies did not show a dose-response relationship. Only folate deficiency was examined in animal models of AD or PD, and the results showed a synergistic effect with PD or AD pathology. Folate appears to protect against oxidative damage associated with ApoE deficiency. Folate and B12 deficiency also induce presenilin-1, but do not appear to affect APP. Thiamine (vitamin B1) is required for active transport of pyruvate across the BBB and maintaining integrity and normal permeability of BBB and folate is protective against homocysteine-induced cerebrovascular damage.

B Vitamin Intervention Trials

Vitamin B1. Five studies – three randomized controlled trials (RCTs), one non-randomized comparative trial (N-RCT), and one uncontrolled cohort study – on the effect of thiamine

intervention among people with either probable or possible AD were heterogeneous in their outcomes. Most found improvements in cognitive function or a slowed rate of deterioration using some measures of cognitive testing, either compared to control or in uncontrolled studies. However, either no difference between treatment and control or no improvement with thiamine was found in all studies with other measures of cognitive function. Only the uncontrolled cohort study reported blood levels of thiamine before intervention and after intervention, and the study included AD subjects with normal mean levels of thiamine.

Vitamin B2. No prospective trial has evaluated the effect of B2 treatment on neurocognitive function.

Vitamin B6. Only two RCTs of cognitively intact populations investigated the effect of B6 intervention on cognitive function. Participants had B6 levels within normal range in both trials. With treatment, a significant improvement was found with one cognitive function test. It is also unclear whether the changes with treatment were significantly different than changes in the control arm. No other significant change was reported in the studies.

Vitamin B12. Five RCTs, one non-randomized comparative trial, and seven cohort studies assessed the effect of B12 intervention on cognitive function in humans. Two RCTs, one non-randomized comparative trial, and four cohort studies recruited participants with low B12 levels, while the rest of the studies assessed individuals with normal B12 levels. There was a large degree of heterogeneity in populations, levels of B12 deficiency, dose, route of administration, and cognitive function assessment instruments. Although several of the studies showed some improvement in cognitive function, few reached statistical significance. Among studies that assessed similar populations after implementing the same tests, results were frequently conflicting. Several cohort studies revealed significant improvement while fewer cohorts reported a significant decline in scores for cognitive function. However, the interpretation of these studies is difficult because they analyzed subjects with variable courses of dementia over time, without comparing to control groups. Vitamin B12 was given intramuscularly in the only RCT that found a significant effect in the treatment group compared with the controls. Similarly, only cohort studies that used intravenous or intramuscular vitamin B12 reported a significant effect on cognitive function scores. However, given the lack of data directly comparing oral and injected routes of vitamin B12 and the paucity of controlled trials limits any conclusions regarding the utility of different routes of administration. Some indirect evidence showed that demented or cognitively impaired patients with short duration of treatment for dementia or short disease duration might benefit more than patients with treatment or disease of longer duration if they use B12.

Folate. Five studies (three RCTs and two uncontrolled cohort studies) reported data on the effect of folate intervention among normal people or those with dementia, cognitive impairment, or PD. One RCT among subjects with dementia and normal folate levels found worse neuropsychological scores in the folate treatment group among subjects with dementia. Two other studies – one RCT and one uncontrolled cohort study – found statistically significant improvement in the folate treatment compared with placebo group among demented, cognitive impaired, and normal subjects. The study of patients with PD found no therapeutic benefit. Three

studies reported blood folate levels before intervention; of which only two studies (one RCT and one uncontrolled cohort study) included patients with low folate levels.

Combination of B vitamins. Six studies (three RCTs and three uncontrolled cohort studies) assessed the effects of a combination of B vitamins as interventions on cognitive function. All used different daily doses of various B vitamins including folate, B6, and B12. Five of the six studies found no significant change in cognitive function after combination B vitamin supplementation. Only one of the uncontrolled cohort studies found a significant, large benefit. Only one RCT assessed the effects of combined vitamin intervention on patients with low blood folate levels; other studies included patients with normal mean blood vitamin levels.

Overall. There is weak evidence of a possible benefit of thiamine supplementation in people with AD. There is also weak, and inconsistent, evidence that treatment with injected vitamin B12 is of benefit among those with recent diagnoses of AD or cognitive impairment, particularly if low B12 levels have been documented. The effect of treatment with both B6 and folate is unclear. A single study of B6 found possible improvement with treatment. While studies of folate treatment among demented, cognitive impaired, and normal subjects did find an improvement in cognitive function with folate, one study of patients with dementia did find a worsening on neuropsychological testing with folate compared to controls. Combination treatments with folate, B6, and oral B12 overall were of no benefit. A single study found no benefit of folate treatment for PD. No studies evaluated vitamin B2.

B Vitamin Dietary Intake Studies. Five longitudinal studies and five cross-sectional studies examined the association between the dietary intake levels of B vitamins and cognitive function or the risk of age-related neurodegenerative diseases. No significant associations were found between dietary intakes of B6 or B12 and PD, AD, cognitive functioning, or cognitive decline across three studies. One additional study found higher dietary intakes of B6, B12, and folate were associated with improvements in some, but not all, cognitive function measures. In three separate studies, folate intake was not associated with PD or AD; however, in one study, higher folate intake from food sources and/or supplements was associated with a faster rate of cognitive decline after adjusting for multiple risk factors. Among the five studies cross-sectional studies, only two found any significant associations. One found that subjects with low intake of vitamins B1, B2, B6, and folate, but not B12, scored significantly worse on verbal memory than those with relatively high intake levels. Another also found an association between vitamin B2 intake and cognitive testing in women, but not men. No association between dietary intake of B12 and cognitive function or diagnosis of AD was found in all five cross-sectional studies.

B Vitamin Status Studies

Vitamin B1. Overall, eight cross-sectional studies evaluated levels of thiamine among AD, cognitively impaired, and PD patients. Thiamine levels were measured in plasma, cerebrospinal fluid (CSF) or autopsied brain. Three studies reported significantly reduced mean thiamine levels in the plasma or brain among AD subjects, and one reported a similar reduction in mean levels of thiamine among PD subjects. However, none of the studies that showed significant results adjusted for potential confounders. The remaining four studies found no differences among the investigated groups.

Vitamin B2. Two cross-sectional studies assessed B2 levels among AD or PD and control groups, which included mixed dementia, vascular dementia, and normal subjects. The study of AD subjects reported no significant difference in riboflavin levels among the groups. The study comparing PD to dementia without stroke found lower B2 levels among those with PD. Neither study adjusted for confounders.

Vitamin B6. Ten studies of various designs examined the potential association of B6 serum levels with the diagnosis of dementia or cognitive impairment, or cognitive function. Only one longitudinal cohort study showed a significant correlation between higher levels of vitamin B6 at baseline in cognitively intact subjects and better performance in the figure copying test after 3 years of follow-up. No other significant correlations were found.

Vitamin B12. Thirty-three studies investigated a potential association between serum B12 levels and cognitive function or diagnosis of several types of dementia and cognitive impairment. Most of the studies focused on AD. Thresholds for B12 deficiency varied across studies. Based on the few longitudinal studies, serum B12 levels are not associated with the risk for developing AD or dementia. However, two of the longitudinal studies reported a correlation between serum vitamin B12 levels at baseline and cognitive function status at the end of follow-up among cognitively intact subjects. Other studies that implemented a cognitive function assessment instrument did not support an association between serum B12 levels and cognitive function. Among cross-sectional studies, there was a trend for B12 serum levels to be lower in patients with AD or other types of dementia, which in certain studies reached statistical significance. However, this trend was not consistent. An inverse correlation between B12 levels and duration of AD was reported by one study. Overall though, there is limited evidence for populations with PD, AD, and vascular dementia. Potential factors such as genetic mutations, or disease severity that may affect B12 levels were analyzed by few studies without revealing any consistent effect.

Folate. Thirty four studies examined folate levels assessed in the red blood cells, plasma, serum, CSF, and blood. Fifteen studies examined the association between folate levels and future cognitive function; ten of the studies were longitudinal and the remainders were case-control or cross-sectional with single time-point analyses. All the studies consistently reported either lower mean folate levels or higher prevalence of folate deficiency among subjects with AD and/or cognitive impairment. Overall, one-third of the studies adjusted for possible confounders. Among studies that assessed the association between folate levels and cognitive function, four longitudinal studies and one case-control study reported a statistically significant association between lowest quantile of folate level and cognitive decline after adjusting for possible confounders. One other case-control study reported significant inverse association of folate with cognitive function. Two studies reported no difference in folate levels between subjects with PD and controls.

Overall. The association between thiamine status and age-related cognitive disorders is unclear. Half the studies found no associations and half found lower levels among AD, cognitively impaired, and PD patients. However, none of these studies could differentiate between cause (low thiamine levels resulting in disease) and effect (changes due to disease, including nutritional intake, resulting in low thiamine levels). The studies also failed to adjust for potential confounders. The cross-sectional studies of B2 found no association with diagnosis of AD, but

low levels among people with PD. The large majority of B6 studies found no association between B6 status and the diagnosis of dementia or cognitive impairment, or cognitive function. A large number of studies have evaluated both B12 and folate status. The better, longitudinal studies of B12 failed to find an association with diagnosis or severity of disease. While trends toward lower B12 levels among people with AD were found in cross-sectional studies, these associations were not consistent and proper adjustment for potential confounders was rarely performed. Both the longitudinal and case-control studies of folate status mostly reported an association between low folate levels (defined differently in different studies) and future diagnosis of AD and/or cognitive impairment. No association with PD was found.

Adverse Events. Among the 39 articles reporting on 43 cohorts of subjects taking B vitamin supplements, only 10 reported any information on adverse events. Of these, only two reported that any adverse events occurred. Thiamine was tolerated well in four studies; although initially high doses caused mild gastrointestinal complaints. One of three folate studies reported mild, possibly neurological complaints, that may have been associated with the subjects' PD. No adverse events were noted in one B12 study and in two combination B vitamin studies. No studies reported adverse events for B2 or B6.

Berries

This report includes evaluations of whole berries, berry extracts, and constituents of berries that were derived directly from the fruits. The following berries were included: bilberry, black raspberry, blackberry, blueberry, boysenberry, cranberry, currants, gooseberry, lingonberry, marionberry, raspberry, and strawberry. However, evidence was found for only bilberries, blueberries, boysenberries, cranberries, currants, gooseberries, and strawberries.

Constituents of Berries. Only a limited number of the numerous constituents in berries have been examined separately from the rest of the fruit. These include tannins, anthocyanins and phenolics, from various berries.

Mechanisms of Action. All studies related to mechanisms of action of berry constituents (or whole berries) have been performed in animal or in vitro models. Among 18 animal or in vitro studies (with 19 experiments) investigating berries and neurocognitive function or processes, four studies examined the effects of specific berry constituents on animal performance in neurocognitive testing or on brain biochemistry. The remaining 14 studies (with 15 experiments) used berry extracts that supplemented normal diet or added to in vitro media.

Effects of the constituents in berries. One study showed that intraperitoneally injected bilberry extract containing anthocyanins significantly increased rat brain uptake of triiodothyronine (T3). A second study measured the concentrations of 18 plant tannins, including blueberry, red currant, and gooseberry, generally inhibit brain protein kinase C to a similar degree; although the biological significance in live animals of this in vitro inhibition is unknown. The third study demonstrated that that the anthocyanins in blueberry extracts were able to cross the BBB and the number of the total anthocyanins measured in the brain is associated with rats' learning performance. The fourth study compared the effects of specific berry constituents on neurocognitive outcomes. Rat performance suggested that there is a range of effectiveness associated with the different berry extracts. However, it does not appear that the anthocyanin

component is solely responsible for these improvements. Of note, both the third and fourth studies found no significant effect on rat performance in the Morris Water Maze compared berry to control groups.

Effects of berry extract supplementation. Berry extracts were used to supplement animals' diet or added to in vitro study media in 14 studies with 15 experiments that examined animal performance in neurocognitive testing or brain biochemistry or histology. Of these, two studies used specific animal or in vitro models of AD The remaining 13 studies used adult or aged rat models. Most studies were of good quality. All of these studies were from the same group of investigators.

Only strawberry and blueberry extracts were used to examine the effects of extract supplementation on animal performance in neurocognitive testing or brain biochemistry or histology using a normal-aging rat model. Blueberry and strawberry extract supplementation showed positive or protective effects on almost all biochemical markers and histology findings examined in the rat brain, although only some of the neurocognitive tests and psychomotor functions were significantly improved in these berry-extract-fed rats.

Only two studies used models of AD to examine the effects of various berry extracts. The results suggested that it may be possible to reduce both the deleterious effects of dopamine and the putative toxic effects of amyloid β via various berry extracts as shown in the in vitro study. Results from the animal study that used mice transgenic for amyloid precursor protein and presenilin-1 mutations to model human AD showed that the blueberry extract supplementation seemed to have prevented the deficits in Y-maze performance seen in the transgenic animals fed the control diets, although it did not affect amyloid β deposits.

Human Studies. Only one study evaluated any association between berry (or berry constituent) intake and neurocognitive function. A case-control study of patients with PD, their siblings, and their spouses found that the preference to consume blueberries or strawberries was not statistically significantly associated with presence of PD

Adverse Effects. The single human study of berry consumption was retrospective, therefore no study provided data regarding adverse events from berries in the setting of neurocognitive disorders.

Limitations

An important limitation to the review of age-related neurocognitive disorders is that only scant research in either humans or animal or in vitro models has been performed related to movement disorders and motor symptom degeneration related to PD and associated diseases.

Animal and In Vitro Studies

Rodents are the animals most commonly used to model human cognitive dysfunction or age-related cognitive deficits, but many of the behavioral paradigms employed for evaluation of rodent cognitive abilities or functions are fairly different from those generally assessed in humans.[193] Furthermore, many confounding factors, such as housing conditions, strain, gender, diet, biological rhythms, "stress," and route of drug administration can affect test data

significantly.[194] There remain substantial controversies surrounding the research findings from animal models of cognitive dysfunction. In particular there is no sound empirical basis for making cross-species generalizations about the neural structures that mediate performance in tasks used to assess memory.[193] This is most relevant when comparing animal models to human diseases. In addition, the measured outcomes in animal models are indirect measures of the psychological construct in any test of cognitive function. Therefore, the measures of animals' performance in "cognitive tests" are generally not direct or pure measures of cognitive function. For example, age-related deficits in the Morris Water Maze may not be restricted to learning and memory, but may also include deficits in attention, the ability to process spatial information, and the ability to develop efficient spatial search strategies.[187] It is clear that methodology and procedures of animal models of human cognitive dysfunction are very complex. It is important to avoid simplistic overgeneralizations and inappropriate interpretations of data from animal models of human cognitive dysfunction or age-related cognitive deficits, although this research has generated valuable information about the possible neurobiological basis of the cognitive deficits.

There are a number of limitations specific to our review of the B vitamin and berry literature. The large majority of studies measured performance in otherwise healthy rodents who were made severely deficient in B vitamins. While these studies might elucidate which B vitamins are required for maintenance of brain function, they rarely addressed the question of the actual mechanism of action of the B vitamins. Furthermore, the link between severe vitamin deficiency in normal rodents and the effect of relative vitamin deficiency on human age-related neurocognitive disorders is generally tenuous. Particularly in the case of thiamine deficiency, which is known to result in Wernicke's encephalopathy, the association with AD (or PD) is difficult to ascertain. Studies that linked vitamin deficiencies, vitamin supplementation, or berry supplementation to specific mechanisms of action on nervous tissue were rare and generally provide only a patchy picture of their potential effects.

A major limitation to the data on the potential effects of berries on neurocognitive function is that almost all the studies have been performed in a single laboratory. Replication or similar studies performed by independent groups are necessary before firm conclusions about the putative effects of berries can be made. The constituents in berries that may be responsible for the observed effects on neurocognitive function have yet to be found and the possible mechanisms of action have yet to be fully elucidated.

There remains considerable disagreement about the most meaningful way to assess study quality in human studies, with few analyses attempting to validate specific quality measures. The assessment of study quality in animal and in vitro studies, though, is still in its infancy. No studies have been reported that quantitatively assess the factors that may bias these studies. However, it is clear that improved study design and reporting are necessary.

Human Studies

Only a single, retrospective, human study of berries and PD has been reported. Thus it is clearly premature to assess the association between consumption of berries or berry constituents and age-related neurocognitive disorders.

Among the human B vitamin studies, the majority were of poor quality. The majority of data come from cross-sectional studies, most of which provided only univariate analyses. Even under the best of circumstances cross-sectional studies cannot differentiate between cause and effect.

Thus any associations between B vitamin status and either diagnosis of AD, PD or dementia, or severity of disease may equally be caused by changes in nutrition due to the diseases as by effects of B vitamins on brain function. Many of the associations may also be spurious, since studies rarely attempted to correct for potential confounders such as nutrition status, inflammation status (e.g., homocysteine level), diet, duration of disease, age, sex, genotype, and other factors.

Among the trials of B vitamin supplementation, a large number were either non-randomized comparative trials or non-controlled studies of various designs. These studies are clearly deficient for an adequate assessment of the potential value of B vitamin supplementation. Even among the RCTs the quality of the studies was often poor due to incomplete reporting of methodology and results, lack of blinding, small sample size, short duration, and various other factors.

All the B vitamin studies as a group also suffered from lack of standardization of B vitamin measurement technique, of tissue source (blood, plasma, serum, red blood cell, and cerebrospinal fluid), of normal ranges for B vitamins, of definitions of diagnoses of various dementias, and of tests of cognitive function. In addition, on the order of 50 different tests or subtests were used across the studies. These tests measure different or overlapping domains of cognitive function. Comparisons across studies was thus very difficult. There is also scant evidence regarding the effect of B vitamins on PD.

Future Research

Human Studies

Due to either the limited amount of available data or the poor quality of the bulk of the research to date, future well-performed, well-analyzed, large, prospective studies would be necessary to address all the questions posed regarding the effects and associations between either B vitamins or berries and age-related neurocognitive function. However, standardization is clearly needed both in the areas of vitamin research and in neurocognitive disease. Assuming that additional studies are deemed worthwhile by the research community, these future studies should use only well-verified and commonly used measurement techniques for B vitamin status, and where no standardization has yet been agreed upon, this should be a priority. This may require additional research to verify the value of measurement tools for neurocognitive function. Future studies should also use only well-established diagnostic criteria for neurocognitive disorders and should use only measures of cognitive function that have been verified and are commonly used. Studies that use non-standard diagnostic definitions or neurocognitive tests are of limited value to clinicians, policy makers, and other researchers.

Common to most bodies of evidence regarding medical fields, better quality, well-reported, larger and longer duration studies are needed to address the questions of interest. We strongly recommend that all future randomized trials – including those of B vitamins and potentially of berries or berry supplements– use the CONSORT statement as a guide to reporting (www.consort-statement.org).[195,196] This will not only improve the readers' understanding of the trials, but should also improve the quality of published studies. The value of non-randomized, and particularly non-controlled, trials is limited.

Further cross-sectional studies evaluating the association between B vitamin status and either diagnosis or severity of disease, with few exceptions are of very limited value. Only those that

could include additional data that would give an indication as to cause and effect might be warranted. Additional longitudinal studies are needed to address the questions of the effect of B vitamin status on development of neurocognitive disorders or on the severity of disease. These should either be well-conducted dietary studies using well-established food frequency questionnaire techniques or well-powered, sufficiently analyzed long-term prospective studies. All of these studies of correlations must use appropriate statistical tools, including adjustment for potential confounders and investigation of interactions and sub-groups.

Regarding evaluation of berries and berry constituents, if the animal and in vitro research is deemed to be of sufficient merit to warrant a human study, we would strongly recommend that these studies be more of practical than theoretical value. Trials of extreme diets (i.e., of large daily quantities of berries) or of supplementation with large quantities of berry constituents would not be practical for anyone but research subjects. Even though these studies might help to explain mechanisms of action, they would fail to provide reasonable guidance for those seeking to either prevent or slow neurocognitive decline. Both dietary and supplementation studies should be of doses that a normal person can both easily incorporate into their lifestyle and afford.

Animal and In Vitro Studies

Animal or in vitro models are especially suitable for investigating the mechanisms of actions of factors that might affect the aging process and the accompanying neurodegenerative changes in human, because the contribution of genetic and environmental factors to the aging process can be strictly controlled in animal or in vitro studies.

Several questions of interest will continue to be difficult to address from human studies given ethical and practical limitations. Topics of particular interest that may be more suitable to animal research include sorting out the independent effects of elevated homocysteine and of low B vitamin levels and/or intake, and clarifying the relative harm of B vitamin deficiency (or benefit of B vitamin supplementation) in different stages of health or neurocognitive disease. Several large observational studies in humans have attempted to address the interaction with homocysteine, however, without the ability to closely control homocysteine and B vitamin levels (or intake) it is unlikely that human studies will definitively answer this question. In addition, for practical reasons, it has been very difficult and thus rare that human studies are able to control sufficient factors to allow full analysis of B vitamin status and neurocognitive status.

Unfortunately many of the tasks or tests available to assess the processes underlying the age-associated deterioration of learning and memory have not been validated. Some insights for future aging research using animal or in vitro models were described in details elsewhere.[193,194,197] Here we summarize their recommendations for future research of age-associated cognitive deficits or normal aging:

1. Identify learning and memory tests that are suitable for longitudinal investigations.
2. Replicate all test conditions.
3. Select behavioral or functional models suitable for testing two or more species. This will enable the comparison of data across species and encourage inter-species comparative studies.
4. Select two or more models, each thought to measure the same cognitive process. This will enable evaluation of the concurrent validities of those models.
5. Measure as many different aspects of performance as possible in as great a resolution as possible.

6. Measure learning/memory as a function of degradation of critical stimuli and/or increasing task difficulty. This will enable estimation of the construct validity of the model.
7. Measure mnemonic and non-mnemonic (such as attention) performance in the same animal in the same test session. This allows a comparative approach to assess the cognitive processes in animals that appear to be activated in humans when performing cognitive tests.
8. Take into account the effects of individual animal variability. Ideally, use a single-subject repeated measures design.

In particular, regarding future studies of berries and berry constituents, future research should elucidate the specific constituents that might be responsible for the observed effects on neurocognitive function. For both berry and B vitamin studies, when possible, experiments should evaluate both the specific mechanisms of action and neurocognitive function, allowing a correlation to be made between the two. However, the need for future animal and in vitro studies to evaluate putative mechanisms of action should be assessed largely based on whether clinical benefits of B vitamins and or berries are found in human trials.

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List of Acronyms and Abbreviations

Abbreviation	Description
🧍	Narrowly applicable study (referable to population category)
🧍🧍	Moderately applicable study (referable to population category)
🧍🧍🧍	Broadly applicable study (referable to population category)
+	Normal animals performed better than B vitamin-deficient animals
0	No difference between groups
–	Normal animals performed worse than B vitamin-deficient animals
↑̄	Higher score indicates better cognitive function
↓̲	Lower score indicates better cognitive function
Quality Score: A	Good quality study, least susceptible to bias See Chapter 2, Methods
Quality Score: B	Fair quality study, more susceptible to bias See Chapter 2, Methods
Quality Score: C	Poor quality study, most susceptible to bias See Chapter 2, Methods
%tile	Percentile
?	Unclear reporting
Aβ	Amyloid β-peptide
AD	Alzheimer's Disease
ADAS	Alzheimer disease assessment scale
adj	Adjusted
Aged Ctrl	When compared to the aged controls
AHRQ	Agency for Healthcare Research and Quality
An	Anthocyanin
APP	Amyloid precursor protein
ApoE	Apolipoprotein E
β	Slope for the multivariate linear regression model
B	Blueberry extracts
BB	Blueberry extracts
BBB	Blood brain barrier
BC	Black currant extracts
Blessed	Behavioral rating according to Blessed et al
BS	Boysenberry extracts
Bt	Blueberry extracts, tif-blue
btw	Between
BW	Body weight
Bw	Blueberry extracts, wild
By	Boysenberry extracts
C	Cranberry extracts
CAB	Commonwealth Agricultural Bureau (Abstracts)
CAMCOG	Cambridge Subscale of CAMDEX, assesses orientation, language, memory, praxis, attention, abstract thinking, perception and calculation (includes MMSE)
CAMDEX	Cambridge Examination for Mental Disorders of the Elderly
CB	Cranberry extracts
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CGIC	Clinical Global Impression of Change
CI	Confidence interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
CTA	Conditioned taste avoidance
Cx	Control
DRS	Dementia Rating Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders

Abbreviation	Description
EEG	Electroencephalography
eNOS	Endothelial nitric oxide synthase
EPC	Evidence-based practice center
ERK	Extracellular-signal-regulated-kinase
F344	Fischer 344 mouse strain
FFQ	Food frequency questionnaire
FRAP	Ferric-reducing ability of plasma
FTD	Fronto Temporal Dementia
GBS	Gottfries-Brane-Steen scale
GLUT-1	Glucose transporter protein
GTPase	Guanosine triphosphase
Haycox	Behavioral scale of Haycox
HCl	Hydrochloride
Hcy	Homocysteine
HDS	Hasegawa's Dementia Rating Scale
HSP70	Heat shock protein 70
IC_{50}	Concentrations of compound required for 50 percent inhibition of enzyme
IDDD	Interview for Deterioration in Daily living activities in Dementia, caregiver assessment of functioning in the past week, subscales for initiative and performance;
IGF	Insulin growth factor
IM	Intramuscular
INR	International normalized ratio
IOM	Institute of Medicine
i.p.	Intraperitoneal
IQ	Intelligence quotient
IV	Intravenous
M1AchR	Muscarinic receptor subtype 1
MMSE (-K)	Mini-mental status examination (for Koreans)
mo	Month(s)
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MTHFR	Methylene tetrahydrofolate reductase
MTP	Matching-to-position
MWM	Morris water maze
N	Number of subjects
N/A	Not applicable
NBM	Nucleus basalis magnocellularis
NCCAM	National Center for Complementary and Alternative Medicine
nd	Not documented / no data
NF-κB	Nuclear factor-kappa B
NIH	National Institutes of Health
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NMTP	Nonmatching-to-position
N-RCT	Non-randomized comparative trial
NS	Non-significant
N-Sase	Neutral sphingomyelin-specific phospholipase
ODS	Office of Dietary Supplements
OR	Odds ratio
ORAC	Oxygen radical absorbance capacity
PD	Parkinson's disease
pFe	After irradiation with ^{56}Fe
Ph	Total phenolics
PKC	Protein kinase C

Abbreviation	Description
PLP	Pyridoxal-5'-phosphate
po	Orally
PS	Presenilin
RAVLT	Rey Auditory-Verbal Learning Test
RAWM	Radial Arm Water Maze
RBC	Red blood cell
RCT	Randomized controlled trial
RDA	Recommended Daily Allowance
Ref	Reference group for comparisons
RMBPC	Revised Memory and Behavioral Problems; 3 subscales for memory, depression, and disruptive behavior
RMT	Randt Memory Test
RR	Relative risk (risk ratio)
Rx	Treatment
S	Strawberry extracts
SD	Standard deviation
S-D	Sprague-Dawley
SDAT	Senile dementia of the Alzheimer's type
SE	Standard error
SKT	Syndrom Kurztest, a short cognitive test for assessing memory and attention
SNCA	Alpha-synuclein gene
Stroop	Stroop Color-word Test
T3	Triiodothyronine.
TBARS	Thiobarbituric acid-reactive substances
TD	Thiamine deficient/deficiency
TDP	Thiamine diphosphate
TEP	Technical expert panel
TMP	Thiamine monophosphate
TPP	Thiamine pyrophosphate
Tx	Treatment
Tufts-NEMC	Tufts-New England Medical Center
UL	Upper Limit
unadj	Unadjusted
USDA	US Department of Agriculture
VCAM-1	Vascular cell adhesion molecule
WAIS (-R)	Wechsler Adult Intelligence Scale (- Revised)
WHO	World Health Organization
WMT	Wechsler verbal memory test
wk	Week(s)
Young Ctr	Compared to the young controls
yr	Year(s)

APPENDIXES

to

"B Vitamins and Berries and Age-Related Neurodegenerative Disorders"

Prepared by the Tufts-New England Medical Center Evidence-based Practice Center

(Contract #290-02-0022)

Appendix A. Literature Search Strings

B Vitamins (Feb 2, 2005)

Ovid MEDLINE® <1966 to Jan Week 3 2005>
Ovid MEDLINE® Daily Update <Jan 31, 2005>
Ovid MEDLINE® In-Process & Other Non-Indexed Citations <Jan 31, 2005>
CAB Abstracts <1973 to Dec 2004>

#	Search History	Results
1	exp nervous system diseases/	1259232
2	exp Delirium, Dementia, Amnestic, Cognitive Disorders/	93503
3	neuron$.mp.	329067
4	nerve cell$.mp.	7813
5	alzheimer$.mp.	46029
6	lewy bod$.mp.	2629
7	brain.mp.	639058
8	dementia.mp.	48550
9	neurodegen$.mp.	17734
10	or/1-9	1822067
11	exp folic acid/	21806
12	(folate or folic acid or pteroylglutamic or folacin).mp.	28501
13	exp Riboflavin/	9878
14	(Riboflavin or lactoflavin).mp.	11051
15	exp Thiamine/	9522
16	Thiamine.mp.	11080
17	exp Vitamin B 12/	11454
18	cobalamin$.mp.	2944
19	cyanocobalamin$.mp.	1297
20	exp Vitamin B 6/	10645
21	exp PYRIDOXINE/	8461
22	(pyridoxal or pyridoxamine or pyridoxine).mp.	17309
23	(vitamin adj1 ("B1" or "B 1" or "B2" or "B 2" or "B6" or "B 6" or "B12" or "B 12")).mp.	26741
24	or/11-23	84479
25	10 and 24	11080
26	limit 25 to English language	8984
27	limit 26 to (addresses or bibliography or biography or case reports or clinical conference or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or "review of reported cases") [Limit not valid in: CAB Abs; records were retained]	1762
28	26 not 27	7222
29	remove duplicates from 28	**6640**

Berries (Mar 3, 2005)

Ovid MEDLINE® <1966 to Feb Week 4 2005>
Ovid MEDLINE® Daily Update <Mar 02, 2005>
Ovid MEDLINE® In-Process & Other Non-Indexed Citations <Mar 02, 2005>
CAB Abstracts <1973 to Jan 2005>

#	Search History	Results
1	exp nervous system diseases/	1265160
2	exp Delirium, Dementia, Amnestic, Cognitive Disorders/	94198
3	neuron$.mp.	331088
4	nerve cell$.mp.	7842
5	alzheimer$.mp.	46489
6	parkinson$.mp.	42926
7	lewy bod$.mp.	2651
8	brain.mp.	642015
9	dementia.mp.	48839
10	neurodegen$.mp.	18012
11	or/1-10	1837302
12	limit 11 to English language	*1483695*
13	exp blueberry plant/	33
14	blueberr$.mp.	3182
15	cranberr$.mp.	1275
16	lingonberr$.mp.	176
17	bilberr$.mp.	554
18	marionberr$.mp.	11
19	exp vaccinium/	5126
20	vaccinium.mp.	5781
21	strawberr$.mp.	15298
22	exp fragaria/	12515
23	fragaria.mp.	12692
24	raspberr$.mp.	5253
25	blackberry.mp.	1209
26	ribes.mp.	4419
27	currant$.mp.	3972
28	boysenberr$.mp.	116
29	or/13-28	*30056*
30	exp Flavonols/	6888
31	flavonol$.mp.	3880
32	exp flavonoids/	48492
33	flavonoid$.mp.	27766
34	proanthocyan$.mp.	1545
35	anthocyan$.mp.	8069
36	leucoanthocyan$.mp.	294
37	catechin$.mp.	5272
38	epicatechin$.mp.	1849
39	quercetin$.mp.	7303
40	myricetin$.mp.	765
41	procyan$.mp.	1024
42	flavonol$.mp.	3880
43	biflavonoid$.mp.	635
44	flavanone$.mp.	2305
45	flavonolignan$.mp.	101

#	Search History	Results
46	flavan-3-ol$.mp.	406
47	phytochemical$.mp.	5036
48	exp cinnamates/	10537
49	cinnamate$.mp.	2988
50	hydroxycinnamate$.mp.	507
51	chlorogenic$.mp.	2546
52	Kaempferol$.mp.	2550
53	Rutin$.mp.	3963
54	Hydroxyethylrutoside$.mp.	329
55	cyanidin$.mp.	1253
56	malvidin$.mp.	419
57	petunidin$.mp.	221
58	phloridzin$.mp.	611
59	delphinidin$.mp.	588
60	ferulic$.mp.	3010
61	peonidin$.mp.	342
62	resveratro$.mp.	1819
63	Pulchellidin$.mp.	3
64	or/30-63	*76600*
65	12 and (29 or 64)	*2627*
66	exp nervous system/	1082233
67	limit 66 to English language	928559
68	(12 or 67) and (29 or 64)	3496
69	70 not 66	*875*
70	pterostilbene$.mp.	44
71	(flavan$ or tannin$ or phytonutri$).mp.	17564
72	(70 or 71) and (12 or 67)	361
73	76 not (66 or 69)	*221*
74	exp gooseberry/	24
75	gooseberr$.mp.	1431
76	(74 or 75) and (12 or 67)	19
77	81 not (66 or 69 or 73)	*18*
78	exp fruit/	44312
79	fruit$1.mp.	290648
80	"fruit fly".mp.	4006
81	(78 or 79) not 80	299608
82	87 and 12	1016
83	89 not (65 or 68 or 72 or 76)	*922*
84	or/65,69,73,77, 83	**4633**

Appendix B. Sample Data Extraction Forms

Human Intervention Studies

Author, Year:	**Ref ID**:	**Vitamins**:
Objective:		

Study characteristics	**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Age:				AD:
Country:	%Male:				PD:
Setting:	Race:				VascDz:
Funding:	Other:				Other:
Comments:					

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
		N enrolled:				
		N analyzed:				
		Drop-outs (%):				
Follow-up duration:		Reasons for drop out:				
Comments:						

Primary outcome(s):	
Secondary outcome(s):	
Adverse events:	
Limitations:	
Quality (A/B/C):	Applicability (1/2/3):

Outcome(s):	**Results (Text) (or Definition)**

(Separate table for each outcome)

Outcome **(units)**

		N (Intervention) (Dose)	N (Intervention) (Dose)	N (Intervention) (Dose)	N Control
Baseline value	**(SE/SD)**				
Final value	**(SE/SD)**				
Difference	**(SE/SD/95% CI)**				
***P* Difference**					
Net Difference	**(SE/SD/95% CI)**				
***P* Net difference**					
(RR/OR/HR)	**95% CI**				
***P* (RR/OR/HR)**					

IN THIS TABLE, REPLACE ITEMS IN PARENTHESES WITH ACTUAL ITEMS (EG, Vitamin B6, SE, RR)
REMOVE PARENTHESES!! DOSE GOES IN TOP LINE. 2nd CELL IS FOR SE or SD

Human – Correlation Studies

Author, Year:	**Ref ID**:	**Vitamins**:
Objective:		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS/Longitudinal	Age:		Cases:	Cases:	AD:
	Non-c/Comparative	%Male:				
	Pro/Retrospective	Race:				PD:
Country:		Other:		Controls:	Controls:	VascDz:
Setting:						Other:
Funding:						
Comments:						

Predictor(s): (eg, B vit level)	Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
		N enrolled:			
		N analyzed:			
		Drop-outs (%):			
Comments:					

Other predictors/outcomes reported:	
Follow-up duration (if applicable):	
Reasons for drop out (if applicable):	
Limitations:	
Quality (A/B/C):	Applicability (1/2/3):

Outcome(s):	Results (Text)

Appendix B. Sample data extraction forms
Human correlation studies

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	(Sr/CSF) Mean	(B vit) SE/SD	(unit) r=	*p*	(Sr/CSF) Mean	(B vit) SE/SD	(unit) r=	*p*	(Sr/CSF) Mean	(B vit) SE/SD	(unit) r=	(Sr/CSF) Mean	(B vit) SE/SD	(unit) r=	*p*

IN THIS TABLE, REPLACE ITEMS IN PARENTHESES WITH ACTUAL ITEMS (EG, Vitamin B6, SE, RR)
REMOVE PARENTHESES!!

Description of (Sub-) Groups	N	(Outcome) OR (Adj 1*)	(Outcome) OR (Adj 2*)	N	(Outcome) OR (Adj 1*)	(Outcome) OR (Adj 2*)
(Reference gp)		1	1		1	1
(Reference gp)		1	1		1	1

* Adj 1, adjusted for …

Animal and In Vitro Studies

Author, Year	
Central hypothesis/Stated Purposes of Study	
Hypothesis diagram	
Experimental diets or reagents	
Control diets or reagents	
Study characteristics	Country: Funding source:
Gap in Knowledge	Known: Unknown:
Experimental model	
Study design	
Final sample size	
Duration	
Measurements / Endpoints / Outcomes of interest	
Other outcomes reported	
Results	
Authors' Conclusions	
Quality	
Limitations / Comments	

Appendix C. Evidence Tables

B Vitamin Evidence Tables – Animal / In Vitro Studies

Thiamine

Author, Year	Jolicoeur, 1979 (2 publications)
Central hypothesis/Stated Purposes of the study	To devise a standard battery of tests capable of quantitatively characterizing ataxia in the laboratory rats
Hypothesis diagram	Thiamine deficiency → ataxia indicated by lower performances on a standard battery of tests
Experimental diets or reagents	Thiamine-free diet (ICN Life Sciences, Nutritional Biochemical)
Control diets or reagents	Standard rat chow (Purina Rat Chow) in daily rations equivalent to the amounts consumed by the thiamine deficient animals
Study characteristics	Country: Canada Funding source: Conseil de la Recherche en Sante du Quebec and the Medical Research Concil of Canada
Gap in Knowledge	Known: Chronic deficiency of vitamin B1 results in pervasive metabolic and biochemical alterations in the nervous system. Thiamine deficiency induces a peripheral neuropathy of the "dying back" type which involves both sensory and motor nerve fibers. When rats are chronically fed a thiamine-free diet, a variety of disturbances such as anorexia, poloerection, tremors, kypokinesia and ataxia develop at about 30-40 days from the start of the diet. Unknown: Standard method and procedure for detecting and measuring ataxia in experimental animals has not been developed.
Experimental model	Male Sprague Dawley rats, 275-350 g in weight
Study design	Parallel experiment-controlled study
Final sample size	Control: 6 Thiamine-free: 6
Duration	44 days
Measurements / Endpoints / Outcomes of interest	Locomotor activity: spontaneous locomotor activity was measured for 3 minutes by means of a photocell activity apparatus Catalepsy: Intensity of catalepsy was determined by placing the animals' front paws on a horizontal bar (1 cm in width) suspended 10 cm above the table. Time spent in the position, up to a maximum of 60 seconds, was recorded. Rigidity: the rat was suspended by its front paws grasping a metal rod (0.5 cm diameter) which was held by the experimenter about 50 cm above the table. The time the animal remained on the bar (maximum 60 sec) was recorded. Landing foot spread: After staining the handpaws with ink, the animal was held horizontally 30 cm above a table covered with absorbent paper. The rat was dropped and the distance between the prints of each hindlimb was measure. Gait analysis: After staining the hindfeet with ink, the animal was walked through an enclosed 90 cm long corridor with a paper covered floor. When 2 consecutive strides were obtained, the stride width, length and angle between consecutive steps on contralateral sides were calculated. Reflexive responses: The presence of the righting and corneal reflexes as well as of a normal reaction to tail pinch was verified.
Other outcomes reported	
Results	Statistical analysis indicated that only transient and sporadic effects were produced during initial phase (days 7, 14, 21, 27, and 33) of the thiamine deficiency (TD). On day 21, TD animals displayed significantly less locomotor activity than pair fed controls. A significant decrease in locomotion was also found on day 33 but not on day 27. The gait angles and widths of deficient animals were respectively decreased and increased on day 27 while length of stride was unchanged. On day 33 stride length was significantly decreased in TD rats but the other 2 gait parameters remained unaffected. During days 35 to 44, all TD animals lost the righting reflex, displayed impaired weight shift responses, and eventually died. These effects were not seen in pair fed controls. No significant group differences group differences were found for activity, catalepsy, rigidity, and landing foot spread. Also, aside from the righting reflex and weight shift responses, no other reflexes were affected in TD animals. Finally, gait analysis revealed that in TD rats the angle and length of strides were significantly smaller than those of pair fed controls.
Authors' Conclusions	Thiamine deficiency did not yield similar neurobehavioral effects as acrylamide- or 3-acetyl pyridine-induced ataxia. Only the

	righting reflex and weight shift response were similarly affected by both TD and pyrithiamin treatment. However, all 3 components of gait were disturbed in both TD animals.
Quality	B
Limitations / Comments	Purina rata chow was not an appropriate control diet. The composition of diets prepared using crude materials are known to fluctuate from a batch-to-batch. Thus, it is difficult to obtain reproducible data.

Thiamine

Author, Year	Zimitat, 1990
Central hypothesis/Stated Purposes of Study	To differentiate between the contributions of alcohol consumption and thiamine deficiency to the pathogenesis of Wernicke's encephalopathy. Evaluate acute neurological disease by histology.
Hypothesis diagram	EtOH +/- Thiamine deficiency → Wernicke's encephalopathy
Experimental diets or reagents	1. Thiamine fortified: purified solid diet, thiamine 50 mg/Kg, water to drink 2. Thiamine fortified/EtOH: purified solid diet, thiamine 50 mg/Kg, 15% EtOH in water (ad lib) 3. Thiamine deficient: purified solid diet, thiamine 0 mg/Kg (implied), water to drink 4. Thiamine deficient /EtOH: purified solid diet, thiamine 0 mg/Kg (implied), 15% EtOH in water (ad lib)
Control diets or reagents	Cereal based solid diet, thiamine 8 mg/Kg, water to drink
Study characteristics	Country: Australia Funding source:Government
Gap in Knowledge	Known: Wernicke's encephalopathy associated with both thiamine deficiency and EtOH abuse Unknown: The independent effects of thiamine deficiency and EtOH on neuropathology
Experimental model	Wistar rats, 9 wk, female (6/cage, light/dark cycle 12 hr each, 23° C, mesh floors and feeders washed 3x/wk to prevent coprophagy and fecal contamination)
Study design	Divided into 5 diet groups. Evaluated 3x/wk for food and fluid intake, clinical signs of neurological disease. Brains harvested either when displayed signs of opisthotonus and were moribund (thiamine deficient) or at age 44 wk
Final sample size	Clinical evaluation/Brain histopathology: Thiamine fortified: 12/6; Thiamine fortified/EtOH: 12/6; Thiamine deficient: 18/5; Thiamine deficient/EtOH: 18/6; Control: 12/5
Duration	35 wk
Measurements / Endpoints / Outcomes of interest	Ataxia; Opisthotonus; Moribund state or death; Brain pathology
Other outcomes reported	Diet intake, weight gain, brain weight and volume, biochemistry
Results	Control and thiamine fortified rats showed no signs of clinical disease. Starting at 5-10 wk, all thiamine deficient rats eventually developed ataxia, opisthotonus, and moribund state. Control and thiamine fortified rats: 1 in each group had brain hemorrhage, rest had no abnormality on histopathology. Thiamine deficient rats: 4/11 had no abnormality, 7 had hemorrhages, of which 3 had necrosis (1 mild, 1 severe) and 2 had vacuolation. Pathologies seen primarily in the medial vestibular nucleus
Authors' Conclusions	Symptoms and pathology due to thiamine deficiency (not EtOH). (Symptoms and pathology due to thiamine deficiency exacerbated and hastened by EtOH.)
Quality	B
Limitations / Comments	? of value for age-related neurodegenerative disease Primary purpose of study is to investigate Wernicke's encephalopathy. However, comparison of EtOH to water diets not included here.

Thiamine

Author, Year	Terasawa, 1999
Central hypothesis/Stated Purposes of Study	To evaluate the influence of thiamine on learning ability of rats.
Hypothesis diagram	Thiamine → role in nervous function → learning ability
Experimental diets or reagents	Modified AIN-76 with thiamine HCl 30 mg per 100 g
Control diets or reagents	Modified AIN-76 with thiamine HCl 60 mg per 100 g (normal intake)
Study characteristics	Country: Japan Funding source: Government
Gap in Knowledge	Known: Thiamine plays a role in nervous function, possibly as part of nerve Na channel Unknown: Thiamine effect on learning
Experimental model	Wistar rats, weighing either 260-300 g Electrodes placed in periaqueductal gray matter. Trained to press lever to stop electrical stimulation (which causes escape behavior)
Study design	While on normal diet taught to stop electrical stimulation by pressing a lever positioned in an L maze. One training session / day. Then divided into 2 groups, one continuing normal diet, other given low thiamine diet.
Final sample size	5 in each group
Duration	~42 days after start of low thiamine diet (until rats stopped responding to stimulus)
Measurements / Endpoints / Outcomes of interest	Response time: Time from start stimulation until start action (escape behavior) Running time: Time from start action until presses lever Task completion time: Response time + Running time
Other outcomes reported	none
Results	Normal thiamine rats: Response time, Running time, and Task completion time all remained over time. Low thiamine rats: Response time: For about 3 weeks, remained stable, then progressively slowed until stopped responding Running time: Similar pattern to response time; running time began to slow after response time slowed; observed that rats became more likely to get to lever but not press it.
Authors' Conclusions	Response and running times slowed in thiamine deficient rats. Response time became longer first, then running time.
Quality	C
Limitations / Comments	Poor description of experiment. It appears that rats in normal thiamine group evaluated over whole time period (phase 1 before dividing into groups and phase 2 after division) while rats in low thiamine group analyzed only in phase 2. Appears that this is an experiment testing loss of learning or loss of motor function, since learning done prior to deficiency and may not be testing cognitive function.

Experiment comparing blood thiamine levels in rats without electrode implantation, with electrode but no training, and with electrode with training is not included here.

Thiamine

Author, Year	Ciccia, 2000
Central hypothesis/Stated Purposes of the study	Ethanol and thiamine deficiency (TD) act synergistically, producing more severe clinical neurological disturbances and cognitive and memory impairments than either TD or chronic ethanol alone
Hypothesis diagram	Ethanol + TD → more severe clinical neurological disturbances and cognitive and memory impairments than either TD or chronic ethanol alone [For the purpose of this report, we only focus on the comparison of TD vs. control diet]
Experimental diets or reagents	Animals were treated as control animals except during the 3 episodes of TD, each of which lasted approximately 4.5 weeks. Beginning at weeks 10, 18, and 26 of treatment, the animals were exposed to a bout of TD. During each bout of TD, the animals were fed ad libitum thiamine-deficient chow (Harlan Tekland, Madison, WI) and received intraperitoneal injections of saline 3 times weekly. Each bout of TD was ended by administration of a single dose of thiamine (100 mg/kg body weight, intraperitoneally) and restoration of regular chow.
Control diets or reagents	All animals received ad libitum vitamin-fortified chow and water and were given thiamine (1 mg/kg intraperitoneally) 3 times per week (Monday, Wednesday, Friday)
Study characteristics	Country: US Funding source: No data
Gap in Knowledge	Known: The prolonged and heavy consumption of ethanol has been associated with a wide range of cognitive impairments. TD can induce white matter and more subtle gray matter damage without damaging mamillary bodies. Unknown: Cognitive impairments in chronic alcoholics may be caused by a synergistic interaction between ethanol and TD.
Experimental model	Male Sprague Dawley rats approximately 2 months of age at the start of the study
Study design	Paralleled experiment-controlled study
Final sample size	Control: 14 TD:12
Duration	8 months (including 3 times TD periods; each TD period lasted about 4.5 weeks)
Measurements / Endpoints / Outcomes of interest	Behavioral testing: spontaneous activity, spontaneous alternation, nonmatching-to-position (NMTP), delayed NMTP, reversal learning of matching-to-position (MTP), delayed MTP, and reversal learning of NMTP Clinical observations
Other outcomes reported	Body weights
Results	Behavioral testing: At different stages of behavioral testing, 5 control rats and 2 TD rats either died of unknown causes or developed tumors and were killed. Thus, group sizes reported on each behavioral task are different. There was no significant differences in the response time of spontaneous activity between TD and control rats. For spontaneous alternation, the TD group (n=13) made more perseverative choices than the CT group (n=13) but the difference did not reach statistical significance. No significance differences were observed in the percentage of alternations or omissions between the groups. For NMTP acquisition trials, the average performance of all groups was well above chance on the first session and reached 90% accuracy on session 5. Analysis of the group performance across session 1 through 5 revealed a significant effect of session but no significant treatment effect. All of the TD (n=12) and control (n=13) animals reached criterion level of performance. For delayed NMTP trials, there was no difference in the performances on delayed NMTP trials between TD (n=12) and control (n-=13) animals. For first reversal learning MTP, despite extensive training, 1 TD rat failed to reach criterion and all control animals attained criterion within the maximum 30 sessions of training. Analyses of the performance of animals that did learn the task did not show any significant difference between TD and control animals. For delayed MTP trials, the accuracy of the TD group was near chance at the 120 sec delay, whereas the control group accuracy was close to 70%. TD animals (n=10) performed significantly lower than controls on 120 sec delayed trials ($p<0.0001$)

	For second reversal learning, all of the control and TD animals successfully relearned the NMTP task within the allotted number of sessions. There was no significant difference in accuracy over the initial 16 sessions between the groups. For task failure, no control animals failed to meet criterion for each behavioral task while TD animals had an overall failure rate of 9%. Clinical observations: During the course of each bout of thiamine deficiency, animals in TD group developed several clinical signs, including weight loss, slowed activity, ataxia, opisthotonos, and impaired righting reflex. There were no clinical signs of neurological or behavioral disturbances in any group when fed the thiamine-fortified chow.
Authors' Conclusions	About 3 months after cessation of TD treatment, the TD rats had significantly impaired on the long (120 sec) delayed trials of MTP trials. The observation suggest that repeated episodes of TD treatment produced impairment of working memory. However, because we did not provide pair-fed controls for TD treatment, it is possible that working memory deficits may have been caused by caloric reductions rather than the specific effects of TD toxicity. Overall results of the present study demonstrate that TD produced significant learning impairments on the conditional position discrimination tasks. However the percentage of TD animals that demonstrated learning deficits was relatively small (8%).
Quality	B
Limitations / Comments	There are no pair-fed controls for TD treatment, it is possible that working memory deficits may have been caused by caloric reductions (TD rats had significantly less weight at the end) rather than the specific effects of TD toxicity.

B6

Author, Year	**Tunnicliff et al., 1972**
Central hypothesis/Stated Purposes of the study	Increased pyridoxal-5'-phosphate (PLP) concentration might lead to increased stability of some behaviors, this might be observed as decreased in variance in behavioral variability in animals of uniform genetic constitution.
Hypothesis diagram	Dietary B6 → ↑ PLP → ↑ stability of some behaviors
Experimental diets or reagents	Group 1: average 3 μg of pyridoxine HCL a day Group 2: average 15 μg of pyridoxine HCL a day Group 3: average 150 μg of pyridoxine HCL a day The amount of B6 was estimated based on each animal drank approximately 5ml of water and ate about 5 g of food each day
Control diets or reagents	None
Study characteristics	Country: US Funding source: Office of Education, Department of Health, Education and Welfare; National Institute of Neurological Diseases and Stroke, NIH
Gap in Knowledge	Known: Vitamin B6 is the precursor of PLP. There is good evidence that pyridoxine in the diet is eventually converted to PLP in the brian. There is accumulating evidence that dietary vitamin B6 levels can influence behavior. Unknown: Decreasing levels of PLP may result first in its selective unavailability as a cofactor for some processes of neurotransmitter metabolism. It might, therefore, be expected that levels of performance should be selectively affected for certain behaviors under specific dietary conditions.
Experimental model	C57BL/6J and DBA/2J inbred strains of mice (9 weeks old). These 3 inbred populations of mice have been shown to differ on certain behavioral measures, including open-field activity.
Study design	Tested over 5 successive days for 5 min a day in the open-field for locomotor activity, then over a further 5 days for active escape learning, and finally they were tested for passive avoidance learning
Final sample size	50 male animals in each strain were used for the experiments. Group 1: 15 Group2: 20 Group 3: 15
Duration	On diet for 4 weeks
Measurements / Endpoints / Outcomes of interest	1. locomotor activity 2. active escape learning 3. passive avoidance learning Both the mean scores and the variances were computed for each of the 3 behavioral tests
Other outcomes reported	Glutamic acid decarboxylase in brain
Results	Of the 3 tests, only locomotor activity in the open-field is affected by the dietary pyridoxine. For locomotor activity, no significant difference in mean scores, but variances in all 3 dietary groups were significantly different from each other: Group 1 compared to group 2 ($p<0.01$) Group 2 compared to group 3 ($p<0.001$) Group 1 compared to group 3 ($p<0.01$) Variance was greatest in group 2 (15 μg of pyridoxine HCL) and least in group 3 (150 μg of pyridoxine HCL)
Authors' Conclusions	A specified diet has an effect on behavioral variability. Since both the inbred strains of mice were equally effected by the vitamin B6 diets, authors conclude that the response is not the result of some peculiar genetic defect, but is one that involves biochemical systems fundamental to the organism.
Quality	B
Limitations / Comments	No explanation why groups were unbalanced. No control animal Unable to explain a decrease in variances in those animals on the low pyridoxine diet.

B6

Author, Year	Driskell, 1973
Central hypothesis/Stated Purposes of the study	To assess the value of behavioral measurements, brain pyridoxal phosphate, nucleic acid and protein contents and erythrocyte alanine aminotransferase activities as criteria in establishing the vitamin B6 requirement of weanling and sexually mature male rats
Hypothesis diagram	Inadequate vitamin B6 intake → impairments of behavioral measurements
Experimental diets or reagents	The basal diet supplemented with 15, 30, 45, 60, 75, or 90 µg pyridoxine per 15 g diet
Control diets or reagents	A Basal diet containing: (in %) vitamin-free casein, 15, sucrose, 29, cornstarch and vitamin mix, 34.88, cellulose, 2; Jones-Foster (15) salt mixture, 4, hydrogenated fat, 10; L-methionine, 0.08, L-cystine, 0.04, and corn oil with vitamins A, D, and E, 5.
Study characteristics	Country: US Funding source: No data
Gap in Knowledge	Known: Vitamin B6 is needed in prenatal growth particularly by the central nervous system. The brain completes most of its growth during the prenatal period; its maturation is completed early in life. Unknown:
Experimental model	Virgin mature female rats weighing approximately 220 g
Study design	Randomized controlled trial
Final sample size	Control: 6 B6 15, 30, 45, 60, 75, or 90 µg/15 g diet: 6, 6, 6, 6, 6, 6 respectively
Duration	3 weeks
Measurements / Endpoints / Outcomes of interest	Activity and curiosity: Animals were tested in a runway measuring 85 cm long and 23 cm wide. Phtoelectric cells located at the midpoint counted the number of times the animal traversed the runway (activity). A small metal object attached to a metal disk 3.8 cm in diameter was electrically isolated from the floor such that simultaneous contact of the object and floor registered a count (curiosity). Animals were tested during 15-minute intervals on 14 consecutive days. Learning: T maze with water as a reinforcer. Measures obtained were correctness of response choice and latency (time from beginning of a trial to choice by the animal). Emotionality: Fecal boli were counted for each animal during all testing sessions.
Other outcomes reported	Brain composition, including pyridoxal kinase activity, pyridoxal phosphate content, RNA and DNA analysis, and protein analysis) Erythrocyte alanine aminotransferase activity
Results	For sexually mature rats only, curiosity responses were significantly lower in the groups receiving 15 ($p<0.01$) and 30 ($p<0.05$) µg of vitamin B6 daily than in animals receiving higher levels. There is no difference in the curiosity between animals receiving 45, 60, 75, and 90 µg of vitamin B6 daily. For sexually mature rats only, the 15 and 30 µg of vitamin B6 daily groups had significantly lower activity scores ($p<0.01$) than animals on the higher pyridoxine levels. There is no difference in activity scores between animals receiving 45, 60, 75, and 90 µg of vitamin B6 daily. There were no significant differences in maze performance among the dietary groups in sexually mature rats.
Authors' Conclusions	The data obtained in this study indicated that the rat required an intake of 30 to 45 µg of vitamin B6 daily in order to exhibit a stabilized level of activity and curiosity. A simple learning task, as exemplified by the T maze data obtained in this study, reflected no significant difference between the dietary groups.
Quality	A
Limitations / Comments	For the purpose of our report, we only look at the outcomes for sexually mature rats

B12

Author, Year	**Masuda, 1998**
Central hypothesis/Stated Purposes of the study	The effects of egg PC combined with vitamin B12 on memory of nucleus basalis magnocellularis (NBM) lesioned rats in the Morris water maze task, and on choline or ACh concentrations in the brain of NBM lesioned rats
Hypothesis diagram	PC + vitamin B12 → ↑choline or Ach in the brain of NBM lesioned rats →↑water maze performances
Experimental diets or reagents	PC group: control diet plus 10 g/kg of egg yolk PC (PL-100LE, 92% PC; Q/P/ Corp., Tokyo) Vit B12 group: control diet plus 1.0 mg/kg of vitamin B12 (Sigma) PC+Vit B12 group: control diet plus 10 g/kg of egg yolk PC and 1.0 mg/kg of vitamin B12 Egg PC and Vitamin B12 which were dissolved in water were administered orally using intragastric tube for 18 days after surgery (for inducing NBM lesions)
Control diets or reagents	20% casein diet, containing protein (casein: 200 g/kg), carbohydrate (corn starch and sucrose: 675 g/kg), fat (corn oil: 50 g/kg), fiber (cellulose powder: 20 g/kg), mineral mix (40 g/kg), vitamin mix (10 g/kg), DL-methionine (3 g/kg) and choline (2 g/kg)
Study characteristics	Country: Japan Funding source: No data
Gap in Knowledge	Known: Acetylcholine (Ach) is an essential neurotransmitter which plays a role in learning and memory. In AD, the most remarkable change of neurotrasmitters is the decrease of Ach, especially in the cerebral cortex. Several studies have shown the increase of brain choline and Ach contents in rodents. The problem is that learning and memory were not evaluated in these studies. Unknown: The effects of phosphatidylcholine (PC) combined with vitamin B12 on memory of rats.
Experimental model	Male Wistar rats weighing 250-300 g with NBM lesion (one of the animal model which mimics some of the cholinergic hypofunction and memory loss associated with Alzheimer's disease)
Study design	Paralleled experiment-controlled trial
Final sample size	SHAM-Ctrl: 10 NBM-Ctrl: 10 NBM-B12: 10 NBM-PC: 10 NBM-B12+PC: 10
Duration	10-18 days, depending on experiments
Measurements / Endpoints / Outcomes of interest	Spontaneous movements were measured by Animex counter (AUTOMEX II, Columbus Instruments) for 10 min on 3 consecutive days after surgery 10-12 Morris water maze task: on day 14 after surgery, water maze task was carried out. All animals were trained for 3 consecutive days (during days 14, 15, 16 after surgery) Spatial probe (Retention): the next day after acquisition test (on day 17 after surgery), were removed the platform and allowed the rats to swim for 60 sec. The time spent in the west quadrant where the platform had been located during training was measured.
Other outcomes reported	Brian choline and Ach concentrations
Results	There was no significant difference in spontaneous movements of rats between groups. Worris water maze: - Acquisition: The unlesioned SHAM-ctrl group had significantly shorter latencies than the NBM-ctrl group for 3, 4 and 5 blocks ($p<0.05$, NK). NBM-ctrl group remained learning deficit and required 20-30 sec to find the platform, even Latencies of acquisition in NBM-12 group was not statistically different from that of the NBM-ctrl group. - Spatial probe (Retention): In NBM lesioned rats, the time spent in the platform-quadrant was significantly shorter than that in the sham control rats ($p<0.01$, NK) Times of the NBM-B-12 group was not statistically different from that of the NBM-ctrl group.
Authors' Conclusions	Low dose (1 mg/kg) of vitamin B12 alone did not recover the depletion of choline and Ach concentrations in the frontal cortex and did not improve memory of NBM lesioned rats. If shortage of choline in the frontal cortex markedly occurred by NBM lesioning, activation of choline acetyltransferase by vitamin B12 may not be useful for ACh synthesis.

Quality	A
Limitations / Comments	For the purpose of this review, only results from the comparisons of Vit B12 to control groups are considered. Vitamin B12 is usually included 0.05 mg/kg diet (equivalent to about 0.001 mg/kg) in the standard stock diet for rats. Vitamin B12 was dissolved in water were administered orally using intragastric tube, and the duration of intervention was relatively short.

Folate

Author, year	Duan, 2002
Central hypothesis/Stated Purposes of the study	By increasing Homocysteine (Hcy) levels, folate deficiency endangers dopaminergic neurons thereby increasing the risk of Parkinson's disease
Hypothesis diagram	Folate deficiency → ↑Hcy → dysfunction and death in dopaminergic neurons → PD
Experimental diets or reagents	Folate deficient diet (FD diet): diet lacked folate, but was otherwise identical to the control diet.
Control diets or reagents	Standard mouse diet (Dyets, Inc.; diet #518754) which contained 2 mg folate/kg of food.
Study characteristics	Country: US Funding source: ND
Gap in Knowledge	Known: PD is characterized by dysfunction and degeneration of dopaminergic neurons in the substantia nigra resulting in progressive akinesia, tremor and rigidity. Recent findings suggest the Hcy levels are increased in PD patients. Unknown: Whether or not folate deficiency and/or elevated Hcy levels play a critical role in the pathogenesis of PD.
Experimental model	The toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces PD-like pathology and behavioral symptoms model in 2-month-old male C57B1/6 mice weighing 21-23 g
Study design	After 3 months dietary treatments, both experiment and control animals (5-month old mice) received either 2 i.p. injections of 20 mg MPTP/kg body weight, separated by 4 hours, a regiment that resulted in no detectable pathology or symptomology, or saline injections. Behavior testing for motor function was assessed 1 week later. 24-hr later, mice were killed and brains were rapidly removed; the striata were removed and stored at –80 °C until used for measurements of monoamines and metabolites.
Final sample size	FD diet – MPTP 10 FD diet – Saline 10 Ctrl diet – MPTP 10 Ctrl diet – Saline 10
Duration	3 months
Measurements / Endpoints / Outcomes of interest	Motor performance was assessed with a rotary rod apparatus. Both the total time spent on the rotating rod and the total number of falls for each mouse were recorded Number of dopaminergic neurons in substantia nigra: counted TH immunoreactive neurons in the substantia nigra (SN) of each mouse
Other outcomes reported	Plasma Hcy levles Levels of tyrosine hydroxylase (TH; an enzyme required for dopamine synthesis) in the striatum
Results	Folate deficiency alone did not impair performance on rotarod tests. There was no significant difference in the time on the rotarod or in the number of falls between animals on folate deficient diet and those on control diet. Folate deficiency alone did not affect striatal TH levels nor numbers of TH-positive neurons in the SN. FD diet + MPTP injection → marked decrease in TH levels in the striatum; marked 50-60% loss of dopaminergic neurons in the SN ($p<0.01$) → significant decrease in time on the rotarod ($p<0.01$); significant increase in the numbers of falls per 5 min ($p<0.01$)
Authors' Conclusions	In contrast to mice on the control diet that were resistant to the subtoxic dose of MPTP, mice that had been maintained on the folate-deficient diet exhibited profound motor dysfunction as indicated by a decrease in the time period they could maintain themselves on the rotarod and by an increased numbers of falls.
Quality	A
Limitations / Comments	

Folate

Author, Year	*Kim, 2002*
Central hypothesis/Stated Purposes of Study	To investigate the effects of folate deprivation on plasma homocysteine, and its cerebrovascular and neurotoxic effects, we induced hyperhomocystinemia in rats by folate deprivation and examined the morphological alterations in cerebral microvasculature by electron microscopy
Hypothesis diagram	
Experimental diets or reagents	Folate deficient diet (folate-D): Diet #31; Samtaco without added folate
Control diets or reagents	Folate-supplemented diet (folate-S): Diet #31; Samtaco adding 0.004 g folate/kg diet
Study characteristics	Country: Korea Funding source: Government
Gap in Knowledge	Known: Unknown:
Experimental model	Male Sprague-Dawley rats (6-mo-old) (Samtaco, Osan, Korea
Study design	Paralleled experimental-control trial, blinded analyses
Final sample size	8 per group
Duration	8 weeks
Measurements / Endpoints / Outcomes of interest	Electron microscopic findings for cerebrocortical microvascular wall in brain cross sections
Other outcomes reported	Weight gain, food intake, plasma homocysteine levels
Results	Rats fed folate-S diet (control) showed a normal cerebral capillary wall with a relatively smooth luminal surface and a regular thin layer of basement membrane around the endothelium, surrounging a pericyte. A degenerative appearance of the cerebrocortical microvascular wall was shown in rats fed folate-D diet. High amplitude mitochondrial swelling (m) with disintegration of mitochondrial cristae and dissolution of cytoplasmic organelles in the endothelial cell cytoplasm are exhibited. Abnormal electron-lucent structures indicating perivascular amorphous fibrosis are observed within the basement membrane and in the perivascular area. Locally and irregularly thickened basement membrane is also observed in cerebral microvessels of folate-deficient rats. Frequent perivascular detachment was observed in relatively large cerebral microvessels. Characteristic degenerative pericytes including mitochondrial and cytoplasmic swollen profiles are also shown.
Authors' Conclusions	
Quality	A
Limitations / Comments	The folate-S diet is considered "standard diet" or control diet.

Folate

Author, Year	Kruman, 2002
Central hypothesis/Stated Purposes of the study	Folate deficiency and Hcy sensitize neurons to Aβ-induced death
Hypothesis diagram	Folate deficiency and Hcy → increase Aβ-induced death of hippocampal cells → Increase risk of AD
Experimental diets or reagents	Diet lacked folate and contained 4.5 gm/kg D,L-homocysteine (Dyetes Incorporated; diet 518806)
Control diets or reagents	Standard mouse diet that contained defined choline and folate and lacked D,L-homocysteine (Dyets, Incorporated, Bethlehem, PA; diet 518754)
Study characteristics	Country: US Funding source: No data
Gap in Knowledge	Known: In AD the death of neurons in brain regions critical for learning and memory is believed to result from increased production and accumulation of insoluble forms of amyloid β-peptide (Aβ), which may endanger and kill neurons by inducing OS and disrupting cellular ion homeostasis. DNA damage has been documented in association with neuronal degeneration in brain tissues of AD patients. Folate deficiency and homocysteine, which can impair DNA repair in non-neuronal cells. Unknown: Whether folate deficiency and homocysteine can promote neurons to Aβ-induced death
Experimental model	7-month-old amyloid precursor protein (APP) mutant mice. These mice develop age-dependent deposition of Aβ in their brains, which is first evident in the hippocampus and cerebral cortex beginning after 10 months of age.
Study design	7-month-old APP mutant mice and littermate non-transgenic control mice were maintained on either a control diet or a folic acid-deficient diet. After 3 months on the diets, blood was taken and brains were removed.
Final sample size	No data
Duration	3 months
Measurements / Endpoints / Outcomes of interest	ELISA and immuohistochemical analysis of Aβ production or deposition: ELISA for soluble and plaque-associated Aβ1-42 and Aβ1-40 was performed Quantification of hippocampal pyramidal neurons: Nissl-possitive undamaged neurons were counted in the entire extent of the pyramidal cell layer, including regions CA1 and CA3 (CA2 was included in counts for CA3)
Other outcomes reported	Homocysteine levels
Results	Levels of Aβ1-40 and Aβ1-42 were below the limit of detection in non-transgenic mice (data not shown), while the levels were ~4 and 2 nmol/gm wet brain weight, respectively in APP mutant mice that had been maintained on either the control or folate-deficient diets, with no significant differences in levels of either Aβ species between mice on control or folate deficient diets. The ratio Aβ1-42/ Aβ1-40 also was not changed by the folate-deficient diet. Examination of brain sections immunostained with an antibody against Aβ revealed no evidence of extracellular amyloid deposition in APP mutant mice that had been maintained on either diet. The analyses in regions CA3 of hippocampus revealed a highly significant 20% loss of neurons in APP mutant mice on the flate-deficient diet compared with mutant mice on the control diet ($p<0.0001$); however, there was no differences in the volume densities of neurons in region CA1 between the groups.
Authors' Conclusions	Folate deficiency renders hippocampal CA3 neurons in APP mutant mice vulnerable to death by a mechanism that dose not involve increased Aβ production or deposition.
Quality	B
Limitations / Comments	The in vitro experiments in this article were excluded due to mixed folate and methionine deficient media used. No data on the numbers of animals per group

AD gene

Author, Year	Shea, 2002 [2964]
Central hypothesis/Stated Purposes of the study	Folate compensates for the diminished oxidative buffering capacity of brains of apoE deficient mice.
Hypothesis diagram	Beta-amyloid -> generalized oxidative damage -> neurodegeneration ApoE deficiency ?-> free Fe levels -> ↑reactive oxygen species Dietary folate deficiency -> ↑Hcy -> CNS oxidative damage and potentiates beta-amyloid and glutamate neurotoxicity-> neurodegeneration
Experimental diets or reagents	Vitamin-free, basal diet (AIN-76) Fe challenge with Fe (ferric citrate 8 g/kg) [Vitamin E supplement (alpha-tocopherol, 50 IU/kg) not considered experimental diet here] 1. – Folate, + Vit E, – Fe 2. – Folate, – Vit E, – Fe 3. – Folate, + Vit E, + Fe 4. – Folate, – Vit E, + Fe
Control diets or reagents	Vitamin-free, basal diet (AIN-76) supplemented with folic acid (4 mg/kg total diet wet weight) 1. + Folate, + Vit E, – Fe 2. + Folate, – Vit E, – Fe 3. + Folate, + Vit E, + Fe 4. + Folate, – Vit E, + Fe
Study characteristics	Country: US Funding source: ND
Gap in Knowledge	Known: Folate deficiency leads to oxidative damage and neurodegeneration Unknown: The effect of folate on preventing oxidative damage in normal and ApoE deficient mice
Experimental model	1. ApoE^{tm1Une} homozygous knockout mice on a C57B1/6J background, 10-14 mo old 2. Normal C57B1/6J mice, 10-14 mo old
Study design	Mice fed experimental or control diets for 1 month, after which total CNS tissue was harvested, homogenized, normalized according to total protein and aliquots of unfractionated homogenates were analyzed for TBARs
Final sample size	12 mice per experiment
Duration	1 month
Measurements / Endpoints / Outcomes of interest	TBARs, "an end-point index of oxidative damage"
Other outcomes reported	
Results	1. CNS of normal mice did not contain increased TBARS following Fe challenge in the presence or absence of folate. 2. ApoE knockout mice without folate had significantly increased TBARS when challenged with Fe. 3. ApoE knockout mice with folate did not have increased TBARs when challenged with Fe.
Authors' Conclusions	The genetic deficiency of a complete absence of ApoE can be alleviated with folate repletion. This may provide a partial explanation as to why certain ApoE alleles are associated with increased prevalence and earlier onset of AD, yet do not exhibit 100% penetrance.
Quality	A
Limitations / Comments	TBARs are a rough estimate only of oxidative damage. In this experiment they derived from a combination of lipid, protein and DNA oxidative damage. TBARs measured from whole CNS, not just key brain areas related to AD, such as hippocampus and cortex. Experiment does not distinguish between cerebrovascular and neuronal oxidative damage. No "clinical" outcomes.

ApoE, apolipoprotein E, CNS, central nervous system TBAR, thiobarbituric acid-reactive substances.

AD gene

Author, Year	Shea, 2002 [2966]
Central hypothesis/Stated Purposes of the study	Test hypothesis that deficiencies in ApoE function are associated with increased oxidative stress in CNS. Compare responses of transgenic mice lacking ApoE with those of normal mice to dietary oxidative stress induced by folate dprivation (and by inclusion of excess iron within their diet).
Hypothesis diagram	ApoE deficiency ->↑ susceptibility to oxidative damage Dietary folate deficiency -> ↑Oxidative stress -> CNS oxidative damage
Experimental diets or reagents	Vitamin-free, basal diet (AIN-76) supplemented with folic acid (4 mg/kg total diet wet weight) Fe challenge with Fe (ferric citrate 8 g/kg) 1. + Folate, – Fe 2. + Folate, + Fe
Control diets or reagents	Vitamin-free, basal diet (AIN-76) 1. – Folate, – Fe 2. – Folate, + Fe
Study characteristics	Country: US Funding source: ND
Gap in Knowledge	Known: Folate deficiency leads to oxidative damage and neurodegeneration Unknown: The effect of folate on preventing oxidative damage in normal and ApoE deficient mice
Experimental model	1. $ApoE^{tm1Unc}$ homozygous knockout mice on a C57B1/6J background 2. Normal C57B1/6J mice
Study design	Mice fed experimental or control diets for 1 month, after which total CNS tissue was harvested, homogenized, and prepared for measurements
Final sample size	3-4 mice per diet per experiment
Duration	1 month
Measurements / Endpoints / Outcomes of interest	1. TBARs 2. Total antioxidant activity in CNS homogenates in a cell-free assay
Other outcomes reported	Glutathione
Results	1. ApoE-deficient mice had significantly increased TBARs when challenged with Fe in the absence of folate, in contrast to ApoE-deficient mice challenged with Fe in the presence of folate and to normal mice, regardless of folate or Fe status. 2. Antioxidant capacity lower in ApoE-deficient mice receiving Fe in the absence of folate compared to same mice receiving folate or compared to normal mice, regardless of folate status.
Authors' Conclusions	In the setting of ApoE deficiency, mice are incapable of overcoming oxidative stress of Fe without folate. The combined influence of Fe challenge and folate deprivation depletes the antioxidant capacity of ApoE-deficient mice.
Quality	A
Limitations / Comments	TBARs are a rough estimate only of oxidative damage. In vitro antioxidant capacity might not reflect in vivo oxidative capacity. TBARs measured from whole CNS, not just key brain areas related to AD, such as hippocampus and cortex. No "clinical" outcomes.

ApoE, apolipoprotein E
TBAR, thiobarbituric acid-reactive substances.
CNS, central nervous system

AD gene

Author, Year	Shea, 2003 [2968]	
Central hypothesis/Stated Purposes of the study	Deficiencies in ApoE function are associated with increased oxidative stress in CNS. This was carried out by comparing the responses of transgenic mice lacking ApoE with those of normal mice of the identical genetic background to dietary oxidative stress induced by folate deprivation and by inclusion of excess iron within their diet.	
Hypothesis diagram		
Experimental diets or reagents	Vitamin-free, basal diet (AIN-76) Fe challenge with Fe (ferric citrate 8 g/kg)	
	1. + Folate, – Fe	2. + Folate, + Fe
Control diets or reagents	Vitamin-free, basal diet (AIN-76) supplemented with folic acid (4 mg/kg total diet wet weight)	
	1. – Folate, – Fe	2. – Folate, + Fe
Study characteristics	Country: US Funding source: ND	
Gap in Knowledge	Known: Unknown:	
Experimental model	Normal C57B1/6J mice and ApoE homozygous knockout mice on a C57B1/6J background were maintained for one month on a basal diet with and without folic acid; and with or without iron. Homogenates of CNS were measured.	
Study design	Mice fed experimental or control diets for 1 month, after which total CNS tissue was harvested, homogenized, and prepared for measurements	
Final sample size	Samples were derived from 3 to 4 normal and 3 to 4 ApoE -/- mice for each dietary condition, from 3 to 4 separate experiments (total n ≥ 12 for each diet for all 3 experiments)	
Duration		
Measurements / Endpoints / Outcomes of interest	thiobarbituric acid-reactive substances (TBARs) as an index of endpoint oxidative damage Trolox equivalent antioxidant capacity	
Other outcomes reported	glutathione level in CNS	
Results	CNS of ApoE deficient mice demonstrated an approximate 20% increase in glutathione levels compared to normal mice. Individually, deprivation of folate and dietary iron each increased glutathione levels in CNS of both normal and ApoE-deficient mice. In combination, folate deprivation with dietary iron further increased glutathione levels in both normal and ApoE-deficient mice. However, CNS of ApoE-deficient mice displayed a markedly greater increase than did CNS of normal mice under all condtions. ApoE deficient mice displayed increased TBARs when challenged with dietary iron in the absence of folate ($p<0.05$). In the absence of any dietary challenge, CNS of ApoE -/- mice exhibited a significantly increased oxidative buffering capacity vs. that of normal mice ($p<0.05$). ApoE deficient mice receiving iron in the absence of folate displayed less CNS antioxidant capacity than under any other condition for these mice.	
Authors' Conclusions	1. These findings demonstrate that ApoE deficient mice are less capable of buffering oxidative challenge than are normal mice. 2. These findings also suggest that the increased levels of glutathione observed in CNS of ApoE deficientl mice following dietary challenge with iron and folate deficiency were incapable of compensating for the lack of ApoE function. 3. The lack of ApoE activity fostered an increase in one or more endogenous antioxidants. 4. Folate deprivation fostered an additonal increase in antioxidant in normal CNS. 5. Endogenous antioxidants were upregulated in CNS of both strains of mice in response to oxidative stress. 6. The combined influence of iron challenge and folate deprivation depleted the antioxidant capcity of ApoE deficient mice.	

	7. These data support the hypothesis that ApoE deficiency is associated with increased oxidative stress.
Quality	A
Limitations / Comments	

AD gene

Author, Year	Fuso, 2005
Central hypothesis/Stated Purposes of the study	The nutritional deficits could lead to Hcy/SAM metabolism alteration (hyper-homocysteinemia) with the con sequent decrease of SAM levels. Alterations in SAM/Hcy cycle (producing Hcy accumulation) are responsible for decreased SAM (S-adenosylmethionine) levels and, in turn, for reduced DNA methylation.
Hypothesis diagram	Folate and B12 deficient → Hcy cannot transform to SAM → ↑ Hcy and ↓ SAM → reduced DNA methylation → modulation gene expression (such as amyloid precursor protein (APP) processing and ß-amyloid (Aß) production through the regulation of Presenilin1 (PS1) expression)
Experimental diets or reagents	Deprive medium (DDM): It was prepared substracting folate and vitamin B12 from the preparation of F14 medium and used with 1% fetal calf serum plus 10µM retinoic acid. The residual folate and vitamin B12 concentrations were 60 and 2.3 pg/ml, respectively. These vitamin amounts derived only from the fetal calf serum (FCS) added to the medium.
Control diets or reagents	Differentiation medium (DM): F14 medium with 1% fetal calf serum plus 10 µM retinoic acid
Study characteristics	Country: Italy Funding Source: MIUR grants (Ateneo and FIRB 2003)
Gap in Knowledge	Known: Elevated Hcy plasma level is a serious risk factor for the onset of AD. Moreover SAM levels decrease in AD patients and, generally, with aging. The great relevance of Aß production in AD is largely documented and accepted, as well as the importance of reducing this protein in the therapy. Unknown: Correlation between the SAM/Hcy cycle, DNA methylation and AD
Experimental model	2 different neuroblastoma cell lines: SK-N-SH and SK-N-BE. Since the 2 lines gave similar results in all the experiment performed, we decided to show only the results relative to SK-N-BE cell line.
Study design	In vitro
Final sample size	4 or 5 depending on experiments
Duration	N/A
Measurements / Endpoints / Outcomes of interest	PS1 and PS2 expression APP expression
Other outcomes reported	Apoptosis, SAM production, γ- and ß-secretases (BACE) production
Results	Gene expression, compared DM to DDM media: There was no significant difference in APP expression between the 2 groups both at 48 and 96 hours (n=4). PS1 expression was similar in DM while DDM induced high increase in PS1 expression (n=4, $p<0.05$). PS2 expression seems to be independent from the different experimental conditions, but with a little higher variability respect to APP. Protein expression, compared DM to DDM media: The 110-kDa APP isoform increased in DM and was more abundant after 144 hours in all the experimental conditions; nevertheless, there was no significant differences between DM and DDM cells (except for a decrease in DDM after 144 h, $p<0.05$) (n=5). PS1 protein was synthesized at similar levels in DM while DDM induce an increase in PS1 synthesis (n=5, $p<0.05$). PS2 synthesis seems to be independent from the experimental conditions.
Authors' Conclusions	Complete and deprived medium as well as FCS were preliminarily analyzed in order to verify that folate and vitamin B12 content was really low. We think that such a partial vitamin deprivation from the medium, instead of a total depletion, is more representative for a nutritional deficit. The HPLC analysis also allowed us to demonstrate that the intracellular SAM levels of cells grown in deprived medium were lower respect to the complete medium; this findings confirmed that Hcy metabolism alteration due to folate and vitamin B12 deprivation really caused the reduction of SAM levels in the cells.

	We demonstrated that PS1 can be induced by folate and vitamin B12 deprivation. The other genes involved in APP processing and APP itself seemed to be independent on medium deprivation.
Quality	A
Limitations / Comments	For the purpose of our review, the best comparison in this study is DDM vs. DM since the only differences in the contents of the media are the amount of folate and B12. Although growth medium (GM) is the control group in the original study, we should not compare DDM to GM because there is no retinoic acid (or vitamin A) in GM. Furthermore, the results or comparisons regarding the effects of additional SAM in the media are not of interest. Since the authors' primary purposes were not to examine the effects of folate and B12 on the gene expression, the conclusions of the original study focused on the effect of the additional SAM to the media on the gene expression. All measurements were performed in duplicate.

Blood-brain barrier or cerebrovascular endothelial function

Author, Year	Warnock, 1968
Central hypothesis/Stated Purposes of Study	Using labeling patterns of glutamate to study pyruvate metabolism of normal and thiamine deficient rats.
Hypothesis diagram	Pyruvate metabolism (to glutamic acid) that occurs in the liver or the brain result in different radiolabeling patterns of glutamic acid. Therefore, differences in glucose and pyruvate transport across the blood-brain barrier (BBB) can be measured in different conditions.
Gap in Knowledge	Known: As above. Pyruvate does not directly enter the brain of adult animals. Unknown: BBB transport in thiamine deficiency
Experimental diets or reagents	Thiamine deficient diet
Control diets or reagents	Thiamine adequate diet
Study characteristics	Country: US Funding source: Government
Experimental model	Male rats, Sprague-Dawley, initial weights of 50-65 g.
Study design	Parallel experiment-controlled trial
Final sample size	Thiamine deficient: 15 Normal diet: 10
Duration	nd. "At first signs of polyneuritis."
Measurements / Endpoints / Outcomes of interest	Brain glutamic acid radiolabelling 10 minutes after injection with Na Pyruvate-2-^{14}C and decapitation. (If pyruvate is metabolized in the liver, brain glutamic acid would be labeled on carbon 4. If metabolized in the brain, glutamic acid would be labeled mainly on carbon 5.)
Other outcomes reported	Evaluation of rats given thiamine anti-metabolite oxythiamine.
Results	Pyruvate-2-^{14}C entered the brain directly in adult thiamine deficient animals.
Authors' Conclusions	Selective transport across BBB was not functioning in a normal fashion.
Quality	B
Limitations / Comments	Duration of thiamine deficiency not stated, although sufficient to cause symptoms.

Blood-brain barrier or cerebrovascular endothelial function

Author, Year	Robertson, 1971
Central hypothesis/Stated Purposes of Study	To test the hypothesis that the blood brain barrier (BBB) remains intact with respect to plasma proteins in the early edematous lesion associated with thiamine deficiency, but becomes permeable to protein in the necrotic stage.
Hypothesis diagram	
Gap in Knowledge	Known: Early stages of experimental thiamine deficiency causes intracellular edema in brainstem, without morphologic evidence of parenchymal or vascular necrosis. Unknown: Whether early changes are due to a defect of transport of plasma proteins across the BBB directly related to the deficiency.
Experimental diets or reagents	Synthetic thiamine-free diet (Nutritional Biochemical Corp) ad lib
Control diets or reagents	Same diet with thiamine HCl 40 µg/100 g body weight i.p. daily
Study characteristics	From day 28-46, bovine albumin conjugated with fluorescein isothiocyanate (FLA) or complexed with Evans blue (EBA) was administered IV. Animals were killed 30 minutes later. Brainstem and cerebellum were analyzed as transverse frozen sections. Brains were evaluated for both histology (degree of spongy edema, presence of congestion, hemorrhages, tissue necrosis and neuronal loss). Rats were then categorized into: Group A: Slight edema (n=10) Group B: More marked spongy reticulation, frequently accompanied by vascular congestion (n=14) Group C: Hemorrhages, tissue degradation and neuronal fallout. (n=22)
Experimental model	Immature female rats, Long Evans strain or Wistar Furth strain
Study design	Parallel, controlled study.
Final sample size	56 analyzed
Duration	28-46 days
Measurements / Endpoints / Outcomes of interest	Presence or absence of extravascular fluorescence in relation to the severity of lesion (n=46)
Other outcomes reported	Presence or absence of FLA or EBA in neural parenchyma (n=10)
Results	In control animals, specific fluorescence of the neuropil – that is, tissues beyond the vascular confines, was never seen. Extravascular fluorescence was present in 1/24 rat brains from Groups A+B (n=24). Extravascular fluorescence was present in 12/22 rat brains from Group C (n=22). P<0.001 for difference.
Authors' Conclusions	BBB is intact with respect to albumin in the early lesions of thiamin deficiency. Thus intracellular edema associated with early deficiency results from a defect in cell membrane transport rather than a vascular leak of the inflammatory type across BBB.
Quality	B
Limitations / Comments	Initially included 134 rats. Controls were selected in every fifth animal. Rats that died spontaneously (n=51), had perfusion failures (n=5), or had technical failures (n=22) were not evaluated. No breakdown number for animals that were not evaluated per group.

Blood-brain barrier or cerebrovascular endothelial function

Author, Year	Manz, 1972
Central hypothesis/Stated Purposes of Study	To follow up on earlier experiment reported in Robertson, 1971. To further define the nature and sequence of permeability changes of the BBB, using horseradish peroxidase.
Hypothesis diagram	
Gap in Knowledge	Known: Early stages of experimental thiamine deficiency causes intracellular edema in brainstem, without morphologic evidence of parenchymal or vascular necrosis. These changes are not related to disrupted albumin transport across the BBB. Unknown: Other possible transport defects in BBB
Experimental diets or reagents	Synthetic thiamine-free diet (Nutritional Biochemical Corp) ad lib
Control diets or reagents	Same diet with thiamine HCl 40 µg/100 g body weight i.p. daily
Study characteristics	From day 30-45 of thiamine deficiency, horseradish peroxidase was administered IV. 1-6 hours later fixation was carried out with glutaraldehyde and animals were killed. Brainstem was fixed and prepared. Brains were evaluated both histology (edema, hemorrhage, necrosis) and under both light and electron microscopy for peroxidase granules. Rats were then categorized into: Group A: edema only (n=7) Group B: hemorrhage and necrosis. (n=30)
Experimental model	Immature female rats, Wistar Furth strain
Study design	Parallel, controlled study.
Final sample size	49 analyzed (37 treated, 12 controls)
Duration	30-45 days
Measurements / Endpoints / Outcomes of interest	Parenchymatous infiltration with horseradish peroxidase (HRP)
Other outcomes reported	
Results	Under light microscopy 12 control rats and the 7 Group A rats had “qualitatively and quantitatively” the same pattern of peroxidase granules in phagocytes. Among the 30 Group B rats, 21 had a diffuse parenchymatous infiltration of the vestibular area, generally extensive; un unreported number had numerous large plump phagocytic cells within the vestibular area; 9 had linear deposits of reaction product along the course of vessels. 0/7 Group A rats had parenchymatous infiltration, 21/30 Group B rats did; P<0.001 Under electron microscopy, control rats and Group A rats were devoid of peroxidase in the vascular basement membrane and the neural parenchyma. In Group B rats, the interendothelial junctional complexes were morphologically intact; reaction product was deposited in the contraluminal side basement membrane zone of intercellular gaps.
Authors’ Conclusions	Confirms timing of BBB competence from Robertson 1971 study. BBB damage seen in later stages corresponds to damage seen from cold-injury edema and other models of cerebral edema. Leakage appears to be predominantly through the mechanism of pinocytosis (introduction of fluids into a cell by invagination of the cell membrane, followed by formation of vesicles within the cells), not disruption of interendothelial junctions. This may be due to the fact that thiamine is a necessary cofactor for several enzymes required for active transport across cell membranes.
Quality	A
Limitations / Comments	Initially included 99 rats. Rats that died spontaneously (n=21) or presenting technical difficulties (n=29) were not evaluated.

Blood-brain barrier or cerebrovascular endothelial function

Author, Year	Lee, 2004
Central hypothesis/Stated Purposes of Study	To clarify the effects of hyperhomocysteinemia on cerebral endothelial function and elucidate possible mechanisms of homocystine-induced vascular and neuronal toxicity.
Hypothesis diagram	
Experimental diets or reagents	HF diet: AIN93M diet modified to contain folic acid and homocystine (Hcy): 0.3% Hcy and 0.008 g/kg folate
Control diets or reagents	H diet: AIN93M diet modified to contain 0.3% Hcy
Study characteristics	Country: Korea Funding source: Government
Gap in Knowledge	Known: Folate supplementation has proven to be effective in treating hyperhomocystinemia and endothelial dysfunction Unknown: The cerebrovascular effects of homocystine and folate supplementation are poorly understood
Experimental model	Male Sprague-Dawley rats (8 weeks old) (Samtaco, Osan, Korea)
Study design	Paralleled experimental-control trial
Final sample size	
Duration	2 weeks
Measurements / Endpoints / Outcomes of interest	Cerebral expression level of two markers for endothelial dysfunction: the glucose transporter protein (GLUT-1) and vascular cell adhesion molecule (VCAM-1) Endothelial nitric oxide synthase (eNOS): Samples of the brains were analyzed by Western blotting technique
Other outcomes reported	Plasma Hcy, vitamin B12 and folic acid Weight gain, food intake, food efficiency ratio
Results	When the rats with induced hyperhomocysteinemia received 2 weeks of dietary folate supplementaion with homocystine (group HF), the level of brain eNOS protein expression increased by 43.5±5.4% (p=0.04) compared to the 4 week homocystine diet (group (H group). The increase is in good agreement with the 27.4±2.7% (p=0.04) increase in the GLUT-1 level and the 42.9±4.9% (p=0.04) decrease in VCAM-1 level. Note: No significant difference in weight gain, food intake or food efficiency ratio between animals on HF and those on H diets.
Authors' Conclusions	This study shows that hyperhomocysteinemia induces endothelial dysfunction, characterized by reduced eNOS activity with concomitant changes in the VCAM-1 and GLUT content in the rat brain. In addition, these effects were significantly ameliorated by dietary supplementation with folate. To our knowledge, this is the first morphological study to demonstrate the beneficial effects of dietary folate on hyperhomocysteinemia-induced cerebral endothelial dysfunction in vivo. However, in the course of this study, an unexpected result was observed in the cerebral content of the VCAM-1 in the homocystine-fed animals (group H) – this was reduced rather than increase. The cause of this unexpected result for VCAM-1 is currently under investigation.
Quality	A
Limitations / Comments	Rats in folate diet group were fed a diet with Hcy for 2 weeks before changed to folate-supplmented diet. The original control rats were fed a diet without folate or Hcy for 2 weeks and then continued for another 2 weeks. For the purpose of this review, this comparison is not appropriate.

Blood-brain barrier or cerebrovascular endothelial function

Author, Year	Lee, 2005
Central hypothesis/Stated Purposes of Study	To evaluate the effects of 8 weeks of dietary folate supplementation on cerebral vascular damage induced by hyperhomosysteinemia in vivo, in particular investigating the structural features of the cerebral vasculature by electron microscopy.
Hypothesis diagram	
Experimental diets or reagents	HF diet: AIN93M diet modified to contain folic acid and homocystine (Hcy): 0.3% Hcy and 0.008 g/kg folate
Control diets or reagents	H diet: AIN93M diet modified to contain 0.3% Hcy
Study characteristics	Country: Korea Funding source: Government
Gap in Knowledge	Known: Folate supplementation has proven to be effective in treating hyperhomocystinemia and endothelial dysfunction Unknown: The cerebrovascular effects of homocystine and folate supplementation are poorly understood
Experimental model	Male Sprague-Dawley rats (8 weeks old) (Samtaco, Osan, Korea)
Study design	Paralleled experimental-control trial
Final sample size	4 per group
Duration	8 weeks
Measurements / Endpoints / Outcomes of interest	Cerebral expression level of the glucose transporter protein (GLUT-1) Ultrastructural alterations in cerebral vasculature and % of damaged vessels: electron microscopy
Other outcomes reported	Plasma TBARS, Hcy, vitamin B12 and folic acid Weight gain, food intake, food efficiency ratio
Results	8 weeks of folate supplementation significantly increased the cerebral GLUT-1 protein, which had been decreased by homocystine diet for 2 weeks and for 10 weeks ($p<0.05$) In the folate supplemented group damaged vessels such as annihilation of cell organelles, degeneration of mitochondrial bilayer, and perivascular detachment were also observed. Dietary supplementation with folate for 8 week (group HF) reduced the percentage of damaged vessels compared to a homocystine diet for 10 week (group H) but the percentage was still higher than in controls (group C)
Authors' Conclusions	It is likely that folic acid supplementation may reduce cerebrovascular damage induced in hyperhomocysteinemia by affecting cellular oxidative metabolism.
Quality	A
Limitations / Comments	Rats in folate diet group were fed a diet with Hcy for 2 weeks before changed to folate-supplmented diet. The original control rats were fed a diet without folate or Hcy for 2 weeks and then continued for another 8 weeks. For the purpose of this review, this comparison is not appropriate. All rats had induced hyperhomocystinemia before the dietary allocation.

Rejected articles that used immature animal models

Author, Year	Robertson, 1968
Central hypothesis/Stated Purposes of Study	To investigate the ultrastructural features of early brain stem lesions in thiamine-deficient rats
Hypothesis diagram	
Experimental diets or reagents	Synthetic diet devoid of thiamine fed ad lib
Control diets or reagents	Above diet with daily subcutaneous injection of thiamine HCL 4μg/10 gm body weight
Study characteristics	Country: Canada Funding source: Medical Research Council of Canada
Gap in Knowledge	Known: Unknown:
Experimental model	Immature female hooded rats (Quebec Breeding Farms), weighing 50-65 gm at the outset
Study design	
Final sample size	Experimental 114; Isocaloric Controls 38; Equal-Weight Controls 20; Treatment Controls (thiamine deficient animals given thiamine injection for 4 days) 11
Duration	Animals were killed at daily intervals between days 27 & 41 by intracardiac perfusion of 3% glutaraldehyde
Measurements / Endpoints / Outcomes of interest	Behavior; brain lesions
Other outcomes reported	
Results	Thiamine deficient rats appeared well & continued to grow until about the 12th day, after which there was reduction of food intake & gradual loss of weight of about 1.5 gm/day. Neurologic signs first appeared between days 28 & 35; abnormalities of posture and equilibrium were followed in 2 or 3 days by loss of the ability to right themselves when rolled over, and by frequent falling when stimulated to walk. Death followed in 1-3 days unless the animals had been perfused earlier. The control animals receiving daily injections of thiamine displayed no neurologic signs, & apart from weight changes, appeared normal. Of 68 thiamine-deficient rats perfused on Day 27 and subsequent days of the experiment, 37 exhibited neurologic signs, and 32 of these had lesions. In none of the 31 animals killed before neurologic signs appeared were histologic changes demonstrated. By light microscopy, minimal changes were seen in 6 rats, from days 28-33; they consisted of reticulated or vacuolated neuropil, frequent focal swelling s of myelin sheaths and some axon irregularities. In 20 rats (Days 33-36) there were small perivascular hemorrhages & marked edema. Six animals (Days 38-41) exhibited varying degrees of frank necrosis. By electron microscopy, early lesions consisted of swelling of perivascular glial processes, with watery cytoplasm. Subsequently, glial processes & cell bodies away from vessel walls became swollen; fluid accumulation in occasional myelin sheaths give rise to separation of lamellae and distention of the sheaths. Later, there was patchy loss of perivascular glial foot processes. A few foot processes contained small membrane bound vacuoles. Cytoplasm became swollen, cell membranes were discontinuous & organelles underwent disintegration and the extracellular space became markedly enlarged. None of the control rats demonstrated lesions in the brain stem by electron microscopy.
Authors' Conclusions	Not explicitly stated.
Quality	A
Limitations / Comments	

Author, Year	Collins, 1970
Central hypothesis/Stated Purposes of Study	To evaluate the cerebellum in experimental animals rendered thiamine-deficient.
Hypothesis diagram	TD → glycogen accumulation within glial cells in the cerebellar molecular layer → neuronal damage or cerebellar degeneration
Experimental diets or reagents	Complete diet containing 0.25 mg of thiamine per kg of diet. In order to avoid death from the acute effects of thiamine deficiency, the animals were supplemented with intraperitoneal injections of thiamine hydrochloride containing "5γ" of thiamine or with Purina Rat Chow containing the same amount of thiamine.
Control diets or reagents	Pair-fed control: Purina Rat Chow was fed in daily amounts so as to reproduce the weight curve of the experimental animals Normal control: synthetic diet containing 1.0 g of thiamine per kg of diet replaced the Purina Rat Chow
Study characteristics	Country: US Funding source: National Institute of Neurological Diseases and Stroke
Gap in Knowledge	Known: Unknown: The relationship between thiamine deficiency and cerebellar degeneration
Experimental model	Sprague-Dawley albino rats of both sexes weighing 100-120 g
Study design	Paralleled experiment-controlled trial
Final sample size	7 animals (In total? Or in experimental group?)
Duration	30 weeks
Measurements / Endpoints / Outcomes of interest	Clinical signs Histological findings: the sections of the cerebellar vermis were studied by phase microscopy, and thin sections, following staining with lead hydroxide, were studies by electron microscopy.
Other outcomes reported	
Results	Of the 7 animals studied, all showed ataxia at some time during the course of the experiment and were ataxic at the time of sacrifice. Cytoplasmic osmiophilic granules accumulation were found in glial cells in the molecular layer of the cerebellum; much less so in the granular layer; authors stated that this granular material is consistent with glycogen granules based upon their size and staining characteristics. Dendritic spines in contact with and surrounded by glycogen-filled glial processes showed signs of degeneration (the number of identifiable subcellular structures was markedly reduced).
Authors' Conclusions	In thiamine deficient albino rats, marked glycogen accumulation was found within cerebellar glial cells and in some areas this process is associated with neuronal degeneration.
Quality	B
Limitations / Comments	

Author, Year	**Nakagawasai, 2000**
Central hypothesis/Stated Purposes of the study	To further clarify the correlation between changes in the level of SST in the brain, particularly in the hippocampus, and amnesia during TD
Hypothesis diagram	Thiamin deficiency → ↓ SST level in hippocampus → ↓ performance of passive-avoidance learning
Experimental diets or reagents	TD group: completely thiamine-deficient diet (CLEA Japan Inc., Tokyo, Japan) consisted of a basic ratio of 67.6% carbohydrate, 18% protein, and 8% lipid; it was supplemented with various vitamins, except for thiamine, and minerals Single treatment with thiamin HCl: TD rats were given a single thiamine HCl [0.5 mg/rat, subcutaneous (s.c.)] treatment on the 14th or 21st day
Control diets or reagents	Pair-feeding control: the animals were given the same amounts of food as the TD group, however, the food contained 1.6 mg thiamine HCl/100 g of diet (CLEA Japan Inc., Tokyo, Japan). Normal control group: the animals were allowed to freely take a complete normal diet containing thiamine.
Study characteristics	Country: Japan Funding source: No data
Gap in Knowledge	Known: Somatostatin (SST), a neuromodulator in the central nervous system, is rick in the cerebral cortex and hippocampus, which are integrative regions of cognitive function. Intracerebrally administered SST improves impairement of learning and memory of cysteamine-treated, scopolamine-treated, and nucleus basalis magnocellularis-lesioned rats in the passive-avoidance learning test. It has been demonstrated that brain SST is one of the most severely affected systems in patients with AD. Unknown: Brain SST may be suggested to play a facilitatory role in cognitive function
Experimental model	Male Wistar rats, weighting 75-85 g at the beginning of the experiment
Study design	Paralleled experiment-controlled trial
Final sample size	N=8 per group
Duration	25 days
Measurements / Endpoints / Outcomes of interest	Step-through passive-avoidance task: the latency time of the retention trial was measured on the 14th and 25th day after start of the TD diet. Percentage of animals displaying impairment avoidance learning (entering in the dark compartment within 300 s on retention trial) was also recorded.
Other outcomes reported	SST content in the brain
Results	The latency time was not significantly changed on the 14th day as compared TD rats with the pair-fed rats. On the 25th day however, the latency time of the retention trial in the TD rats was significantly decreased as compared to the pair-fed rats ($p<0.05$) The % of avoidance learning impairment of the TD significantly increased on the 25th day ($p<0.05$). The single thiamine HCL on the 14th day reversed the latency time of the retention trial to the control level on the 25th day ($p<0.05$). However, when the thiamine HCl treatment was given on the 21st day, no reversal effect was observed for amnesia estimated on the 25th day.
Authors' Conclusions	The present study showed that the amnesia as determined by passive-avoidance task was gradually induced over time after the start of TD feeding. Furthermore, the present data shows that this impairment of avoidance learning was completely reversed to an almost normal range merely by a single injection of thiamine HCl (0.5 mg/rat, s.c.) at a relatively early TD stage (14 days, and it remained reversed even with the continuation of the TD treatment until the 25th day.
Quality	A
Limitations / Comments	

Author, Year	Stewart et al, 1975
Stated Purpose of the Study	To study the behavioral effects of pyridoxine deficiency in postweanling rats
Hypothesis diagram	
Experimental diets or reagents	Pyridoxine deficient diet
Control diets or reagents	1. Pyridoxine deficient diet supplemented with 30 mg of Pyridoxine HCL/Kg of diet (ad lib) 2. Pyridoxine deficient diet supplemented with 30 mg of Pyridoxine HCL/Kg of diet (pair-fed)
Study characteristics	Country: US Funding source: No data
Gap in Knowledge	Known: Unknown:
Experimental model	Male rats of the Charles River CD strain, 3 wk old and 7 wk old
Study design	See original paper for details regarding the 7 separate experiments. The essential features of the apparatus used in the experiment included a start box, separated from the runway proper by a guillotine door, and a safety box with no grids on the floor at the end of the runway. The entrance to the goal box was also through a guillotine door. Shock could be delivered to the floor of the start box and runway but not to the safety box. At each trial both the doors were raised that activated a light and buzzer that served as a conditional stimulus. The conditinal stimulus remained on between the raising of the doors and the onset of the unconditional stimulus which was an electric shock. Both stimuli remained on until the rat escaped from the runway to the goal box at which time the stimuli were terminated.
Final sample size	See table 1 in original paper
Duration	3-10 weeks, depending on the experiment
Measurements / Endpoints / Outcomes of interest	Avoidance response behavior Motor function (running time) Shock escape task Passive avoidance tack
Other outcomes reported	
Results	1. The acquisition of avoidance response over 6 days showed their means (ANOVA) to differ significantly ($P<0.001$). Scheffe tests showed that the pyridoxine deficient group differ significantly from the two control groups, which did not differ significantly from each other. 2. Dietary deficiency had no effect on avoidance behavior in the developing animal until it had been fed the diet for at least 5 weeks. 3. It took the control rats 15 trials before reaching the criterion of 9 avoidance responses over 10 consecutive trials; it took 27.4 trials in the pyridoxine deficient rats ($P<0.01$) to reach the same criterion. 4. Deficient animals were slower to start running in response to the electric shock throughout the testing, and that both groups of animals showed improvement in their start times over the 30 trials of testing. 5. Using running time as the measure, ANOVA showed that there was a main effect due to diet ($P<0.05$), due to trials ($P<0.01$) and an interaction between trials and diet ($P<0.05$). This interaction was due to the run times for deficient animals being faster than controls for the first block of 5 trials and slower than controls for the remaining blocks of trials. 6. Animals were fed deficient or control diets from weaning until the end of week 8 when they were injected with intraperiotneally with pyridoxine 50 mg/Kg and then tested on the shock avoidance responses. The mean number of avoidance response in the deficient group was smaller than the control ($P<0.01$) at 3 days post injection; the mean number is not significantly different at 7 days. 7. Deficiency was induced in young animals starting at 7 weeks of age, i.e. at 4 weeks beyond the weaning period; the

	deficient diet was continued for 7 weeks in one study, and for 10 weeks in another study. There was no significant difference in avoidance response between the two groups in both studies. 8. Animals in another study were first trained to traverse up the runway for water reward and then punished with electric shock for making this response. ANOVA showed that the deficient animals had significantly faster running times ($P<0.01$). Both groups showed a significant reduction in running time over the 3 days ($P<0.01$).
Authors' Conclusions	Avoidance behavior in rats is affected by pyridoxine deficiency. Five weeks of pyridoxine deficiency was sufficient to produce a deficit in active avoidance learning in the postweanling animals whereas up to 10 weeks of deficient diet ingestion produced no effect on young adult animals. Mild motor impairment was produced in the young pyridoxne-deficient rats but the avoidance learning deficit could not be explained away on this basis, because a deficit in passive avoidance was also produced by the deficiency. Reversal of the deficiency by pyridoxine injection restored the active avoidance learning to normal within 1 week.
Quality	A
Limitations / Comments	

Author, Year	**Guilarte, 1991**
Central hypothesis/Stated Purposes of the study	To quantitatively measure the effects of marginal vitamin B-6 nutrition during gestation, lactation, and postweaning on spontaneous locomotor activity of the developing rat.
Hypothesis diagram	
Experimental diets or reagents	Vitamin B6 deficient diet: 0.7 mg/kg pyridoxine HCl
Control diets or reagents	Vitamin B6 sufficient diet: 7.0 mg/kg pyridoxine HCl
Study characteristics	Country: US Funding source: No data
Gap in Knowledge	Known: B-6 deficiency during gestation and lactation results in abnormal CNS development in neonatal animals and human infants. Unknown: Motor abnormalities, one of the most commonly described consequences of neonatal vitamin B-6 deficiency, have not been systematically studied.
Experimental model	Male pup Long-Evans rats at 14, 28, and 56 days of age
Study design	After 2-3 weeks on the specified diet, female rats were mated with male rats. Within 24 hours of birth, offspring were weighed and litter size culled to 8. Dams and offspring were maintained on their respective diet throughout the study.
Final sample size	N=6 per group
Duration	56 days
Measurements / Endpoints / Outcomes of interest	Locomotor activity measurements: Behavioral data collection was automated using a Digiscan Animal Activity Monitor (Omnitech Model #RXYZCM) coupled to a Digiscan Analyzer (Omnitech Model DCM-8). 1 male pup per litter was randomly selected for behavioral study in the computerized Digiscan system. Measurements on the same rat were obtained at 14, 28, and 56 days of age.
Other outcomes reported	
Results	The analysis of variance with repeated measures revealed that there were no significant dietary treatment effects for any of the locomotor activity variables measured. Further analysis of these overall interactions indicated that animals from the vitamin B6 restricted diet group demonstrated a pattern of hypoactivity at 14 days of age followed by hyperactivity postweaning. This effect is demonstrated for the measurements of horizontal activity, total distance, and number of vertical movements. Data for other behavioral measures showed a similar pattern of locomotor behavior.
Authors' Conclusions	The data clearly show 2 patterns of spontaneous locomotor behavior in the vitamin B6 restricted developing rat. In early neonatal life, vitamin B6 restriction produces a generalized hypoactivity in essentially all measures of locomotor behavior. The novel finding in the present study is that in the postweaning period, at 28, 56, and 196 days of age, the vitamin B6 restricted rats became hyperactive in many of the indices of horizontal, rearing, and stereotypic behavior. The degree of hyperactivity became more apparent as the animals aged with many more indices of locomotor behavior demonstrating hyperactivity.
Quality	B
Limitations / Comments	No proxy measure for how "deficient" of those vitamin B6 restricted rats. Perhaps there is no significant difference in B6 status between the 2 groups. Postweaning rats were used.

Author, Year	**Ezer, 1976**
Central hypothesis/Stated Purposes of the study	Vitamin B12 can promote the synthesis of RNA and of protein plays an important role in brain function, particularly in learning and memory
Hypothesis diagram	Vitamin B12 → promote the synthesis of RNA and of protein → improve learning and memory
Experimental diets or reagents	Animals were fed on a standard diet and vitamin B12 was administered intraperitoneally at doses of 4x1, 4x10, or 4x100 μg/kg
Control diets or reagents	Animals were fed on a standard diet and vitamin physiologic saline or water containing tween 80 was administered intraperitoneally
Study characteristics	Country: Hungary Funding source: No data
Gap in Knowledge	Known: The experimental methods elaborated for the laboratory investigation of the learning process on animals can mainly be divided into 2 groups, either being based on the consolidation of Pawlov's conditioned reflex, or applying Skinner's operant conditioning. Unknown: The effect of vincristine and vitamin B12 on brain function assessed by a new simple method called the tape test, which dose not require expensive instruments.
Experimental model	Female Wistar rats weighing 100-120 g. For those animals were selected (or learning-dull rats), which were unable to remove the tape within 60 s during 3 selections (on 3 successive days).
Study design	Parallel experiment-controlled study
Final sample size	Control 96 Vitamin B12 4x1 μg/kg:36 4x10 μg/kg:36 4x100 μg/kg:84
Duration	N/A (intraperitoneally)
Measurements / Endpoints / Outcomes of interest	Problem-solving ability: the problem-solving times were measured on 4 successive days, with posttrial treatment. The problem-solving times are classified as follows: I (excellent) tearing off the tape in 1-20 s. II (good) tearing off the tape in 21-40s. III (poor) tearing off the tape in 41-59s. IV (without success) failure to tear off the tape in 60s. P.S. index = (sum of problem solving I x 100)/sum of problem solving IV
Other outcomes reported	
Results	There was a dose-dependent effect of vitamin 12 on problem-solving ability in learning-dull rats. The results were expressed in 1-2 and 3-4 trial blocks. The change of P.S. index values (except 1 μg/kg vitamin B12) is significant larger than the control values. The problem-solving times were significantly shorter in rats received higher dose of vitamin B12. Compared to the control animals, the distribution of P.S.T 1-4 trial block in rats received 4x100 μg/kg vitamin B12 was significantly toward shorter time categories ($p<0.01$).
Authors' Conclusions	There is a stimulatory effect of vitamin B12 on problem-solving ability of the learning-dull rats and the effect is dose-dependent.
Quality	B
Limitations / Comments	The statistical methods were not reported. Not sure why the comparison arms are not balanced. Vitamin B12 was administered intraperitoneally

Author, Year	Sasaki et al, 1992; Sasaki et al, 1993
Central hypothesis	Acetylcholine contributes to learning and nicotine may improve learning in an acetylcholine deficient rat (data for this is not extracted in this table). The following data pertains to the effect of vitamin B12 on cognition in rats fed with a choline deficient diet.
Hypothesis diagram	
Experimental diets or reagents	1. choline enriched diet (4 mg/g) 2. choline deficient diet (0 mg/g) 3. choline deficient diet supplemented with vitamin B12 (10 mg/Kg)
Basal Diet	Basal diet: standard rat chow containing 1.6 mg/g of choline chloride
Study characteristics	Country: Japan Funding source: SRF Grant for Biomedical Research
Gap in Knowledge	Known: Unknown:
Experimental model	4 wk old male Wistar rats fed above diets
Study design	On diet for 10 weeks, then tested for passive avoidance learning. Step-through procedure: an apparatus consists of two compartments (one illuminated, one dark) separated by a door; an animal was placed into the illuminated side and, through the door, could enter the dark side which has a grid floor; once all 4 paws are on the grid, an electric shock was delivered. The response latency in entering the dark compartment was measured. This learning was repeated on the 2^{nd}, 3^{rd} and 4^{th} day.
Final sample size	10 in each group
Duration	10 weeks
Measurements / Endpoints / Outcomes of interest	Latency time in Passive avoidance learning
Other outcomes reported	Whole brain choline and acetylcholine
Results	Latency time in choline-deficient supplemented with vitamin B12 rats was significantly longer than that of the choline-deficient rats on the fourth day ($P<0.05$). Vitamin B12 increased tissue weight of the brain and content of acetylcholine in rats fed a choline-deficient diet.
Authors' Conclusions	Vitamin B12 facilitated acetylcholine synthesis or release in the brain and improved the cognitive disturbance.
Quality	B
Limitations / Comments	The improvement of cognitive disturbance may be due to intense input of shock stimuli. The study is not able to separate the learning improvement from increased shock sensitivity in the step-through procedure. Not preferred comparisons. For our purpose of this review, the best comparisons in this coline deficient diet supplemented with B12 vs. choline deficient diet.

Author, Year	Gospe et al., 1995
Central hypothesis/Stated Purposes of the study	The 1st experiment describes the effect of folate deficiency on the histopathology of brain and skeletal muscle. The 2nd experiment compares the growth, food spilling behavior and the concentrations of total folate, cysteine and homocysteine in serum, and of neurotransmitters in the hypothalamus and caudate nucleus from folate-deficient and control mice. The 3rd experiment compares the growth, food spilling behavior and the concentrations of folate, SAM and S-adenosylhomocysteine (SAH) in whole brain and hematologic characteristics of folate-deficient and control mice
Hypothesis diagram	
Experimental diets or reagents	Amino acid based diet supplemented with 0 μmol folic acid for 38 days
Control diets or reagents	Amino acid based diet supplemented with 11.3 μmol folic acid per kg diet for 38 days
Study characteristics	Country: US Funding source: USPHS, USDA & California Experiment Station
Gap in Knowledge	Known: Unknown:
Experimental model	Weanling Swiss Webster female mice
Study design	2 groups of mice of equal mean body weights and randomly assigned to the two diets. Measurement of body weights, amount of food given, spilled by the mice and food left in the feed cup were almost all obtained daily. At the end of the feeding periods, the mice were killed by overdosing with diethyl ether and bled by cardiac puncture. Experiment 1, brains were removed and fixed in formalin for pathologic evaluation. Experiment 2, brains were removed, frozen in liquid nitrogen and weighed, caudate nuclei and hypothalamus were dissected from frozen coronal section. Samples were analyzed for neurotransmitters and their metabolites. Experiment 3, whole brains were frozen and analyzed for total-folate, S-adenosylhomocysteine and S-adenosylmethionine.
Final sample size	Exp 1: 2 from folate-deficient group and 1 from the control group (not clearly reported) Exp 2: 5 in each group (only 4 of each were analyzed, data for one deficient and one control mouse were omitted because they spilled very little food) Exp 3: 7 in each group
Duration	Exp 1: 38 days Exp 2: 37 days Exp 3: 39 days
Measurements / Endpoints / Outcomes of interest	Histological findings Neurotransmitters in the hypothalamus and caudate nucleus from folate-deficient and control mice
Other outcomes reported	Weight loss, food spilling behavior, and the concentrations of total folate, cysteine and homocysteine in serum,
Results	1. After approximately 3.5 wk on the folic-acid deficient diet, growth rate declined and these mice eventually lose weight. 2. In Exp 2, at the end of the 37 day feeding period, folate-deficient animals weighed ~70% of the control mice (p=0.01). This was consistent among the 3 studies. 3. In Exp 2, the cumulative food spilled over the 37 day period in the folate-deficient group was 166 ± 21 g vs. 52 ± 11 g in the control (p=0.0015). 4. In Exp 2, the folate deficient group consumed 219 ± 21 g while the control consumed 174 ± 4 g (p=0.039). Even though the folate deficient animals spilled more food, and gained less weight, they actually consumed more food during the course of the experiment. Similar observations were recorded in Exp 3. 5. Serum folate in the animals fed folic acid deficient diet were reduced to <5% of the control (p=0.0001). 6. Brain and spinal cord showed no apparent pathologic changes in folate-deficient animals. 7. Gastrocnemius and soleus muscles from folate deficient mice showed a reduction in the number of larger fibers compared

	to control mice. 8. Differences in hypothalamic concentrations of norepinephrine, dopamine, or their metabolites between deficient and control mice were not significant. Caudate dopamine levels were reduced by 36% (p=0.04), 3,4-dihydroxyphenylacetic acid (DOPAC) by 48% (p=0.03), and homovanillic acid (HVA) by 43% (p=0.047) in folate-deficient mice. The 5-hydroxyindole acetic acid (5-HIAA)/ serotonin (5HT) ratio was lower in folate deficient mice compared to control (p=0.015). 9. Animals fed folic acid deficient diet had significantly lower whole brain folate and SAM; whole brain folate was 47% lower (p=0.01) and SAM was 40% lower (p=0.035). Whole brain (s-adenosyl homocysteine) SAH was not affected, however SAM (s-adenosyl methionine) /SAH ratio was 43% lower (p=0.047)
Authors' Conclusions	The combination of weight loss and augmented food consumption suggests that folate depletion may reduce the efficiency by which animals utilize dietary nutrients to meet physiological functions, suggesting that an alteration in hypothalamic and/or neuroendocrine function may underlie this effect of folate depletion. In addition, these changes may be due to a folate deficiency induced reduction in nutrient absorption. These studies were designed to characterize the food spilling behavior of folate deficient mice and to determine if it might have a neurochemical basis. Precautions were taken to minimize the effects of diurnal variation on the results of this study. These included housing the mice in a room with a 12 h light dark cycle, feeding and weighing the mice at the same time each day and alternately killing control and deficient mice within a 2 h window at the end of each experiment.
Quality	B
Limitations / Comments	The feeding patterns during the dark cycle were not monitored. Exp 3 has no outcome of interests to this review.

B Vitamin Evidence Tables – Human Studies

Intervention

Author, Year: Abyad, 2002	**Ref ID**: 53	**Vitamins**: B12
Objective: To determine whether dementia is associated with low serum B12 levels and whether treatment of demented patients with low level of serum B12 have any impact on memory		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Prospective longitudinal	Age: 82	N/A	Nursing home residents and outpatients with Dx of dementia and low serum B12 level (<300 pg/mL)	ND	AD:
Country:	Lebanon	%Male: 36	N/A			PD:
Setting:	Nursing home and outpatient clinic	Race:				VascDz:
Funding:	ND	Other:				Other: According to the established criteria
Comments: No definition for dementia type is provided						

Intervention(s):	Control: N/A		**Total**	**Intervention 1**	**Intervention 2**	**Control**
B12: 1000 µg iv daily for 1 week; then weekly for 1 month; then monthly thereafter		N enrolled:	62	62		
		N analyzed:	56	56		
		Drop-outs (%):	6 (11)	8 (14)		
Follow-up duration: 12 months		Reasons for drop out: death: 2; ND: 4				
Comments:						

Primary outcome(s):	Folestein MMSE (23-27: mildly impaired; 19-23: moderately impaired; ≤19: severely impaired)
Secondary outcome(s):	
Adverse events:	ND
Limitations:	No normal (without dementia) control group; small sample size; power calculation not reported
Quality (A/B/C): C	Applicability (1/2/3): 1

Outcome(s):	Results (Text) (or Definition)
MMSE	At 3 months to 12 months of follow-up, 40 /56 subjects improved in their mental status score. Six subjects gained 1,2,3,6, and 9 points, respectively, and essentially normalized their scores. Three patients maintained their score after 1 year of follow-up. The only clinical feature that predicted amelioration in MMSE following treatment was a short duration of pre-treatment mental symptoms

All Subjects

Outcome MMSE (0-100)

		N	B12	1000 µg iv	N (Intervention) (Dose)	N (Intervention) (Dose)	N Control
Baseline value	**(SE/SD)**	56	14.5	7.7			
Final value	**(SE/SD)**	56	15	9.9			
Difference	**(SE/SD/95% CI)**	+0.5		2.12			
***P* Difference**		*ND*					
Net Difference	**(SE/SD/95% CI)**						
***P* Net difference**							

Short Symptom Duration*

Outcome MMSE (0-100)

		N	B12	1000 µg iv	N (Intervention) (Dose)	N (Intervention) (Dose)	N Control
Baseline value	**(SE/SD)**	22	19	5			
Final value	**(SE/SD)**	22	25	4			
Difference	**(SE/SD/95% CI)**	+6		ND			
***P* Difference**		*0.0065*					
Net Difference	**(SE/SD/95% CI)**						
***P* Net difference**							

* MMSE score of patients with short (<12 months) pre-treatment symptom duration; adjusting for age, level of education, or serum B12 level in repeated measures analysis of covariance did not alter the significance of this relationship

Long Symptom Duration**

Outcome* MMSE (0-100)

		N	B12	1000 µg iv	N (Intervention) (Dose)	N (Intervention) (Dose)	N Control
Baseline value	**(SE/SD)**	34	18	4			
Final value	**(SE/SD)**	34	22	2			
Difference	**(SE/SD/95% CI)**	+4		ND			
***P* Difference**		*0.25*					
Net Difference	**(SE/SD/95% CI)**						
***P* Net difference**							

** MMSE score of patients with long (>12 months) pre-treatment symptom duration

Intervention

Author, Year: Aisen, 2003	**Ref ID**: 75	**Vitamins**: Folate, B6, B12
Objective: Effect of multi-B vitamin on Hcy and cognitive function		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	Prospective longitudinal cohort	Age:	70.8+/-9.4		Medically stable, probable AD	Significant renal insufficiency (Cr>1.5 mg/dL), history of B12 or folate deficiency, use of vitamin supplement containing >400 µg folate, regular use of B12 injections, or medications known to influence homocysteine metabolism (eg, methotrexate, azathioprine, phenytoin)	AD:	NINCDS-ADRDA
Country:	US	%Male:	36%				PD:	
Setting:	Clinics	Race:					VascDz:	
Funding:	Government	AD duration:	3.3+/-2.5 yr				Other:	
Comments: Open label								

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Folate 5 mg		N enrolled:	69			
Vitamin B12 1 mg		N analyzed:	63			
Vitamin B6 50 mg		Drop-outs (%):	9%			
Follow-up duration: 8 wk		Reasons for drop out:	nd			
Comments: Compliance, by pill count exceeded 80%						

Primary outcome(s):	Homocysteine level	
Secondary outcome(s):	MMSE, Alzheimer Disease Assessment Scale cognitive subscale (ADAScog), Geriatric Depression Scale	
Adverse events:	No serious adverse events and in no instance was the vitamin regimen discontinued as a result of adverse events. In no instance was an adverse symptom judged to be related to the study intervention.	
Limitations:		
Quality (A/B/C):	C	Applicability (1/2/3): 2

Outcome(s):	**Results (Text) (or Definition)**

Outcome **MMSE** **(0-30)**

		N	Multivitamin		N	(Intervention)	(Dose)	N	(Intervention)	(Dose)	N	Control
Baseline value	**(SD)**	63	19.2	7.0								
Final value	**(SD)**	63	19.3	7.7								
Difference												
***P* Difference**		*NS*										
Net Difference												
***P* Net difference**												
(RR/OR/HR)												
***P* (RR/OR/HR)**												

Lack of association between multivitamin use and cognitive decline (unclear if MMSE or ADAScog) was not affected by controlling for baseline Hcy.

Intervention

Author, Year: Blass, 1988	**Ref ID**: 330	**Vitamins**: Thiamine
Objective: Effect of high dose thiamine on cognitive function in patients with AD		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	Randomized Xover	Age: 72		Dementia clinic with diagnosis of AD	Cerebrovascular disease; Hachinski score (for multi-infarct dementia) >4	AD:	National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for "probable AD"
Country:	US	%Male: 36%				PD:	
Setting:	Specialty clinic	Race: nd				VascDz:	nd
Funding:	NIH, private	Other:				Other:	
Comments:							

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Thiamine HCl 1 g TID	Niacinamide 250 mg TID	N enrolled:	16			
		N analyzed:	11			
		Drop-outs (%):	31%			
Follow-up duration: 3 mo		Reasons for drop out:	2 hospitalized; 3 required antidepressant			
Comments: Randomization performed by pharmacy						

Primary outcome(s):	MMSE, Blessed Score, Haycox Score
Secondary outcome(s):	
Adverse events:	None
Limitations:	Small sample size, incomplete description of sample or outcomes
Quality (A/B/C): C	Applicability (1/2/3): 1

Outcome(s):	**Definition**
MMSE	Mini-Mental State Examination, completed by nurse
Blessed Score	Behavioral rating, completed by nurse (Blessed et al. The association between quantitative measures of dementia and senile change in the cerebral gray matter of elderly subjects. *Br J Psychiatry* 1968; 114:797-811)
Haycox Score	Behavioral rating, competed by caretaker (Haycox et al. A simple, reliable clinical behavioral scale for assessing demented patients. *J Clin Psychiatry* 1984;45:23-4)

Outcome	**MMSE**	**(score)**						
		N	**Thaimine**	**3 g/day**			**N**	**Control (Niacinamide)**
Baseline value	**(SEM)**	11	14.2	(1.4)			11	same
Final value	**(SEM)**	11	15.5	(1.5)			11	14.7 (1.6)
Difference	**(SEM)**	+1.35		(0.67)			+0.54	(0.68)
***P* Difference**		*0.08*					*0.45*	
Net Difference	**(SEM)**	+0.72		(0.14)				
***P* Net difference**		*<0.001*						

Outcome	**Blessed**	**(score)**						
		N	**Thaimine**	**3 g/day**			**N**	**Control (Niacinamide)**
Baseline value	**(SEM)**	11	7.41	(0.81)			11	same
Final value	**(SEM)**	11	7.55	(1.00)			11	6.93 (0.86)
Difference	**(SEM)**	+0.14		(0.64)			-0.48	(0.74)
***P* Difference**		*0.83*					*0.27*	
Net Difference	**(SEM)**	+0.62		(0.52)				
***P* Net difference**		*0.27*						

Outcome	**Haycox**	**(score)**						
		N	**Thaimine**	**3 g/day**			**N**	**Control (Niacinamide)**
Baseline value	**(SEM)**	11	11.1	(1.2)			11	same
Final value	**(SEM)**	11	13.4	(1.8)			11	12.2 (1.4)
Difference	**(SEM)**	+2.29		(1.40)			+1.10	(1.20)
***P* Difference**		*0.13*					*0.40*	
Net Difference	**(SEM)**	+1.21		(0.81)				
***P* Net difference**		*0.17*						

"Subjectively, no important clinical changes were observed in these moderately impaired patients during their 3 months of receiving thiamin (nor with the niacinamide placebo)"

Intervention

Author, Year: Carmel, 1995	**Ref ID**: 10010	**Vitamins**: B12
Objective: Effects of cobalamin replacement on dementia patients		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Cohort	Age: 71		Dementia patients, low cobalamin levels < 190 ng/l	ND	AD:
Country:	USA	%Male: 25				PD:
Setting:	Outpatient facilities for dementia, affiliated w/university & VA medical center	Race: ND				VascDz:
Funding:	Government	Other:				Other:
Comments:	Subjects grouped by DSM-III-R criteria into following categories: probable AD, possible AD, and other dementia; controls include PD w/o dementia; cobalamin assay with reference interval 90-1016 ng/l – established by 332 healthy volunteers					

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Cyanocobalamin 1000 µg IM per wk x 8 wk, then per mo for ≥4 mo		N enrolled:		16*		
		N analyzed:		14		
		Drop-outs (%):				
Follow-up duration: 1 follow-up after 6-8 months therapy		Reasons for drop out:				
Comments: *34 AD pts with low cobalamin levels – unclear how many were actually enrolled. Stated 9 pts fully studied, 7 partially studied, remainder refused further tx, were on cobalamin prior to being studied, or did not comply with tx. CERAD battery pre-treatment found variable degrees of dementia in 13 pts & 3 nondementia pts						

Primary outcome(s):	Neuropsychological outcomes via CERAD battery results including MMSE, 15-item naming task, verbal fluency task, verbal memory task, visuoconstructive task	
Secondary outcome(s):		
Adverse events:		
Limitations:		
Quality (A/B/C):	C	Applicability (1/2/3): 1

Outcome(s):	Results (Text)
Neuropsychologic	**Report only overall improvement/worsening in cognitive testing** (N=14) Improved or became normal – 1 (improvement in several CERAD tasks) No change – 12 Worse – 1 (functional progression of dementia, CERAD results did not change noticeably)

Intervention

Author, Year: Deijen, 1992	**Ref ID**: 10006	**Vitamins**: B6
Objective: Effect of B6 supplementation on memory etc.		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	RCT	Age:	73	73	Male, 70-79 yr, healthy, EtOH<4/day, IQ>80	Drugs that affect B6 metabolism, drugs affecting immune reactivity, B6 supplement within 3 mo, auto-immune diseases, long-acting hypnotics or anti-depressants within 1 mo, drug or EtOH addiction, abnormal chemical/hematological profile, sensory or motor defect that may affect testing.	AD:
Country:	Netherlands	%Male:	100	100			PD:
Setting:	Population	Race:	nd	nd			VascDz:
Funding:	nd	PLP	31	29			Other:
		α-EAST	1.75	1.83			
		IQ	109	111			
Comments:	Subjects paired by age, vitamin B6 status and IQ, then randomized.						

PLP: plasma pyridoxal-f'-phosphate; α EAST: erythrocyte enzyme aspartate aminotransferase activation

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Vitamin B6 (pyridoxine HCl) 20 mg per day	Placebo (identical capsules)	N enrolled:	82	41		41
		N analyzed:	76	38		38
		Drop-outs (%):	7%			
Follow-up duration: 12 wk		Reasons for drop out:	3: illness; 3 were matched subjects to the ill ones			
Comments: Complicated statistical analyses performed. Different for each outcome. Suggests that authors may have been fishing for significant results.						

Primary outcome(s):	Cognitive functioning		
Secondary outcome(s):	Pupil size as measure of mental effort, B 6 status, mood		
Adverse events:	nd		
Limitations:	Non-standardized tests. Questionable statistics. Incompletely reported data.		
Quality (A/B/C):	C	Applicability (1/2/3):	2

Outcome(s):	**Results (Text) (or Definition)**
Associate Learning Task	Test of short term verbal memory, remembering name-occupation pairs (9 pairs)
Associate Recognition Task	Test of long term verbal memory, same as Associate Learning Task with 1 hr delay (9 pairs)
Long Term Memory Storage	Difference (by subtraction) between Associate Learning and Recognition Tasks (what is forgotten) (9 pairs)
Short Term Memory Task (Pupilometry)	Pupil diameter measured during timed memory/visual recognition test. Measures "mental effort" as a combination of phasic pupil response, reaction times and number of correct responses. (41 trials)
Speed of Processing Task (Pupilometry)	Pupil diameter measured during timed task requiring choosing button on opposite corner of displayed marker. Measures "mental effort" as a combination of phasic pupil response, reaction times and number of correct responses (51 trials)

Outcome	**Associate Recognition Task**			**(0-9)**			**Reported graphically**	
		N	**B6**	**20 mg**			**N**	**Placebo**
Baseline value	**(SD)**	38	3.2	(2.3)			38	3.9 (2.1)
Final value	**(SD)**	38	3.3	(2.3)			38	2.8 (2.0)
Difference								
***P* Difference**		*NS*						
Net Difference								
***P* Net difference**								

Outcome	**Long Term Memory Storage (Forget Score)**			**(0-9, low score better)**			**Reported graphically**	
		N	**B6**	**20 mg**			**N**	**Placebo**
Baseline value	**(SD)**	38	0.35	(1.4)			38	0.45 (2.1)
Final value	**(SD)**	38	0	(1.4)			38	0.9 (2.1)
Difference								
***P* Difference**		*P<0.03*						
Net Difference								
***P* Net difference**								

Associate Learning Task: Multivariate one-way ANCOVA did not show a multivariate difference between groups.
Mental Effort Tests: Number of correct responses and reaction times on speed of processing task and memory task were the same for both groups. Pupillary responses were the same for both groups.

Intervention

Author, Year: Fahn, 1974	**Ref ID**: 938	**Vitamins**: Pyridoxine
Objective: Effect of pyridoxine on L-Dopa in patients with PD and severe "on-off" effects		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Prospective longitudinal cohort (Xover)	Age: 53 (40-64)		Idiopathic PD, severe on-off effects such that they could no longer function normally. (Initial excellent response to L-Dopa, then choreic movements developed, then on-off: sudden loss of effectiveness with abrupt onset of akinesia followed by equally sudden return of effectiveness). Stabilized for at least 7 days on L-Dopa or Carbidopa/L-Dopa doses.	(Amantadine discontinued)	AD:
Country:	US	%Male: 60%				PD: nd
Setting:	Clinic (admitted for study)	Race: nd				VascDz:
Funding:	Government, Pharmaceutical	Other: 1.5-3 y L-Dopa 2 post-thalamotomy				Other:
Comments:						

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Pyridoxine 100 mg IM with L-Dopa (1 dose)	L-Dopa alone	N enrolled:	5	5		5
Pyridoxine 100 mg IM with Carbidopa/L-Dopa (1 dose)	Carbidopa/L-Dopa alone	N analyzed:	5	5		5
		Drop-outs (%):				
Follow-up duration: 1 dose each, separated by at least 7 days		Reasons for drop out:				
Comments:						

Primary outcome(s):	Plasma levels of Dopa, homovanillic acid (HVA), 3-O-methyldopa (OMD),
Secondary outcome(s):	Clinical state (not clearly defined)
Adverse events:	
Limitations:	
Quality (A/B/C):	Applicability (1/2/3): 3

Outcome(s):	**Results (Text) (or Definition)**
Clinical state	No alteration in clinical state after a single dose of pyridoxine intramuscularly either while receinving L-Dopa alone or with Carbidopa
HVA, OMD	No change in plasma levels after a single dose of pyridoxine intramuscularly (shown graphically from 9 am to ~4 pm in 3 patients)
Dopa	Dopa consistently decreased slightly with pyridoxine compared to no pyridoxine (shown graphically from 9 am to ~6 pm in 3 patients) Effect not seen with combination Carbidopa/L-Dopa

Intervention

Author, Year:	Fioravanti,1997	**Ref ID**:	10007	**Vitamins**:	Folate
Objective:	To evaluate the effect of folate supplementation on cognitive deficits fo aged patients in a controlled trial				

Study characteristics		Population		Controls	Inclusion criteria	Exclusion criteria	Definitions	
Study design	RCT	Age:	80.25 (5.78)	80.21 (5.45)	Patients recruited among the elderly (70-90 yr) living either at home or in a community and had folate below 3 ng/mL and diagnosed to have mild to moderate severity of cognitive decline as assessed by Global deterioration scale	Patients with gastrointestinal, endocrine, CVD, or renal pathology, diagnosed with depression, with no cognitive decline (MMSE >24) or with a clear diagnosis of dementia (MMSE <16). And also those with regular intake of vitamins or of more than 55g of alcohol	AD:	
Country:	Italy	%Male:	25%	8%			PD:	
Setting:	Community and conducted by authors in an academic setting	Race:	ND	ND			VascDz:	
Funding:	nd	Other: weight in Kg	63.88 (14.42)	57.29 (10.56)			Other: Cognitive impaired	MMSE score 16-24
Comments:								

Intervention(s):	Control:		Total	Intervention 1 Folate	Intervention 2	Control Placebo
Folic acid 15 mg/d po	Placebo similar to the intervention	N enrolled:	30	16		14
		N analyzed:	30	16		14
		Drop-outs (%):	0%			
Follow-up duration: 60days		Reasons for drop out:				
Comments: No cognitive enhancer drugs or other treatments active on the CNS were allowed during the treatment period						

Primary outcome(s):	Randt Memory Test: a multidimensional memory test consisting of 5 different tasks		
Secondary outcome(s):			
Adverse events:	ND		
Limitations:	Small sample and short duration of treatment		
Quality (A/B/C):	B	Applicability (1/2/3):	2

Outcome(s):	**Results (Text) (or Definition)**
Cognitive improvement	Greater folate deficiency at the beginning of treatment was related to greater cognitive improvement after 2 months of treatment. However there was a lack of correlation between severity of folate deficiency and severity of cognitive decline at the baseline evaluation.

Blood folate level at baseline

	N=	Mean	SD
Folate treatment group	16	2.34	0.51
Placebo treatment group	14	2.21	0.68

Outcome	Acquisition and recall (part of Randt Memory Test)	**nd on scale**				
		N	**Folate po**	**15 mg**	**N**	**Placebo**
Baseline value	**(SE/SD)**	16	55.31	12.06	14	62.07	14.70
Final value	**(SE/SD)**	16	59.56	12.53	13	60.85	18.81
Difference	**(SE/SD/95% CI)**						
***P* Difference**		*NS*					
Net Difference	**(SE/SD/95% CI)**						
***P* Net difference**		*<0.007*					
(RR/OR/HR)	**95% CI**						
***P* (RR/OR/HR)**							

Outcome	Delayed recall (part of Randt Memory Test)			**nd on scale**		
		N	**Folate po**	**15 mg**	**N**	**Placebo**
Baseline value	**(SE/SD)**	16	56.06	11.16	14	63.0	15.23
Final value	**(SE/SD)**	16	63.44	13.90	13	63.0	19.27
Difference	**(SE/SD/95% CI)**						
***P* Difference**		*NS*					
Net Difference	**(SE/SD/95% CI)**						
***P* Net difference**		*<0.007*					
(RR/OR/HR)	**95% CI**						
***P* (RR/OR/HR)**							

Outcome	Memory index (part of Randt Memory Test)			**nd on scale**		
		N	**Folate po**	**15 mg**	**N**	**Placebo**
Baseline value	**(SE/SD)**	16	49.25	12.26	14	57.07	15.59
Final value	**(SE/SD)**	16	56.06	13.90	13	56.54	21.38
Difference	**(SE/SD/95% CI)**	NS					
***P* Difference**							
Net Difference	**(SE/SD/95% CI)**						
***P* Net difference**		*<0.002*					
(RR/OR/HR)	**95% CI**						
***P* (RR/OR/HR)**							

Outcome	Encoding (part of Randt Memory Test)			**nd on scale**		
		N	**Folate po**	**15 mg**	**N**	**Placebo**
Baseline value	**(SE/SD)**	15	4.33	2.11	14	5.29	2.33
Final value	**(SE/SD)**	16	4.79	1.72	13	5.08	3.29
Difference	**(SE/SD/95% CI)**	NS					
***P* Difference**							
Net Difference	**(SE/SD/95% CI)**						
***P* Net difference**		*<0.005*					
(RR/OR/HR)	**95% CI**						
***P* (RR/OR/HR)**							

Outcome	Cognitive efficiency (part of Randt Memory Test)			**nd on scale**		
		N	**Folate po**	**15 mg**	**N**	**Control**
Baseline value	**(SE/SD)**	16	3.28	1.77	14	4.25	2.33
Final value	**(SE/SD)**	16	3.91	2.62	13	4.31	2.87
Difference	**(SE/SD/95% CI)**						
***P* Difference**		*NS*					
Net Difference	**(SE/SD/95% CI)**						
***P* Net difference**		*NS*					
(RR/OR/HR)	**95% CI**						
***P* (RR/OR/HR)**							

Outcome	Attention efficiency (part of Randt Memory Test)			**nd on scale**		
		N	**Folate po**	**15 mg**	**N**	**Placebo**
Baseline value	**(SE/SD)**	16	6.40	0.77	14	6.83	1.10
Final value	**(SE/SD)**	16	7.52	1.48	13	6.90	1.24
Difference	**(SE/SD/95% CI)**						
***P* Difference**		*<0.05*					
Net Difference	**(SE/SD/95% CI)**						
***P* Net difference**		*NS*					
(RR/OR/HR)	**95% CI**						
***P* (RR/OR/HR)**							

Intervention

Author, Year: Hsu, 1973	**Ref ID**: 1401	**Vitamins**: B6
Objective: Interaction of B6 and L-DOPA in PD		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Prospective longitudinal cohort	Age:	57-76		Cases: PD, treated with L-Dopa 3-6 g/day during the previous 2 yr	Cases: Cardiac, renal or hepatic disease	AD:
Country:	US	%Male:	nd				PD: nd
Setting:	Outpatient (in metabolic ward)	Race:	nd				VascDz:
Funding:	Private; Merck, Sharp and Dohme	Other:					Other:
Comments:	Trial also done in 4 healthy controls.						

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
L-Dopa 2 g/day x 7 days, Pyridoxine 150 mg/day, days 8-9	none	N enrolled:	5	5		0
		N analyzed:	5	5		0
		Drop-outs (%):				
Follow-up duration: 2 days		Reasons for drop out:				
Comments: Metabolic study						

Primary outcome(s):	Urinary excretion of Dopa and Dopa metabolites (Dopa, Dopamine, dihydroxyphenylacetic acid [DOPAC], Homovanillic acid [HVA])	
Secondary outcome(s):	Parkinsonian symptoms	
Adverse events:		
Limitations:	Small sample size, short duration, clinical outcomes not measured in systematic fashion	
Quality (A/B/C):	C	Applicability (1/2/3): 3

Outcome(s):	Results (Text) (or Definition)
24 hr urinary excretion of Dopa and metabolites	Simultaneous administration of pyridoxine and L-Dopa significantly decreased urinary excretion of Dopa and increased excretion of Dopa metabolites (though dopamine was not significantly increased in 24 hour urine).
Parkinsonian symptoms	Deterioration of symptoms in 2 of 5 patients, manifested by increased tremor, which persisted for 24 hr after discontinuation of pyridoxine.

24 hour urine excretion

	N	DOPA	mg	Dopamine	mg	DOPAC	mg	HVA	mg
Baseline value (SD)	5	51.5	4.3	150.3	50.0	57.0	26.0	211.0	112.3
Final value (SD)	5	35.5	3.1	174.1	51.8	95.3	25.2	318.0	172.5
Difference									
***P* Difference**	*<0.02*			*<0.10 (NS)*		*<0.02*		*<0.05*	

Intervention

Author, Year: Hvas, 2004	**Ref ID**: 1414	**Vitamins**: B 12
Objective: To assess the cognitive function and symptoms of depression in individuals with elevated plasma methyl malonic acid (P-MMA)		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	RCT	Age:	75	74	Elevated plasma methyl malonic acid (P-MMA)	nd	AD:
Country:	Denmark	%Male:	33%	35%			PD:
Setting:	University	Race:	Nd	nd			VascDz:
Funding:	Private and meds Industry	Other: CAMCOG	89	89			Other: Cognitively impaired
Comments:	The Cambridge Cognitive Examination (CAMCOG) assesses broad range of cognitive functions and contains 60 items and in Danish individuals mean score <90 is cognitively impaired						

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Cynacobalamin 1 mg IM	Isotonic sodium chloride 1 ml	N enrolled:	140	70		70
		N analyzed:	140	70		70
		Drop-outs (%):	0%			
Follow-up duration: 4 wk treatment and 3 mo follow-up		Reasons for drop out:				
Comments:						

Primary outcome(s):	The Cambridge Cognitive Examination (CAMCOG); Mini mental Status examination; 12 word learning test	
Description of outcomes	MMSE a score below 25 indicates cognitive impairment; 12 word learning test is sensitive for short term memory	
Secondary outcome(s):	Plasma tHcy	
Adverse events:	nd	
Limitations:		
Quality (A/B/C): A		Applicability (1/2/3): 2

P-MMA and P-tHcy measurement methods available

Outcome(s):	**Results (Text) (or Definition)**

CAMCOG		**(0-100)**			
		N	B 12	1 mg	**N** 1 mg Isotonic sodium chloride
Baseline value	**(SE/SD)**	70	89	:	70 89
Final value	**(SE/SD)**	70			70
Difference	**(SD)**	+1.3		4.8	+1.9 4.3
***P* Difference**		*0.04*			*0.001*
Net Difference	**(95% CI)**	-0.6	(-2.2, +0.9)		
***P* Net difference**		*NS*			

Outcome	**MMSE**	**(0-100)**			
		N	B 12	1 mg	**N** 1 mg Isotonic sodium chloride
Baseline value	**(SE/SD)**	70	26		70 27
Final value	**(SE/SD)**	70			70
Difference	**(SD)**	+0.3		2.3	+0.2 1.7
***P* Difference**		*NS*			*NS*
Net Difference	**(95% CI)**	+0.1		-0.6; +0.8	
***P* Net difference**		*NS*			

12 word learning test, immediate		**0-12**			
		N	B 12	1 mg	**N** 1 mg Isotonic sodium chloride
Baseline value	**(SE/SD)**	70	5		70 5
Final value	**(SE/SD)**	70			70
Difference	**(SD)**	+0.2		1.4	+0.4 1.7
***P* Difference**		*NS*			*0.04*
Net Difference	**(95% CI)**	-0.2		-0.7; +0.3	
***P* Net difference**		*NS*			

12 word learning test, 15 min		**0-12**			
		N	B 12	1 mg	**N** 1 mg Isotonic sodium chloride
Baseline value	**(SE/SD)**	70	2		70 2
Final value	**(SE/SD)**	70			70
Difference	**(SD)**	+0.2		0.35	+0.7 1.7
***P* Difference**		*NS*			*0.001*
Net Difference	**(95% CI)**	-0.5		-1.1; -0.02	
***P* Net difference**		*0.04*			

Intervention

Author, Year: Ikeda, 1992	**Ref ID**: 1431	**Vitamins**: B12
Objective: IV B12 for AD		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Prospective longitudinal cohort	Age: 71+/-13		Alzheimer-type senile dementia or AD	History of serious diseases	AD: DSM III, NINCDS-ADRDA
Country:	Japan	%Male: 40%				PD:
Setting:	Unclear	Race: Japanese				VascDz:
Funding:	nd	Other:				Other:
Comments:						

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
IV mecobalamin 500 μg 3x/week x 8 wk	None	N enrolled:		10		
		N analyzed:		10		
		Drop-outs (%):				
Follow-up duration: 12 wk		Reasons for drop out:				
Comments:						

Primary outcome(s):	MMSE, Mattis' Dementia Rating Scale		
Secondary outcome(s):	Other scales: Modified Gottfries-Brane-Steen scale (M-GBS), Hasegawa's Dementia Rating Scale (HDS), Hamilton Depression Scale, Subjective symptoms, Neurological symptoms, Activities of daily living, Caregiver evaluation, Overall evaluation		
Adverse events:	No side effects were detected in the laboratory tests nor were there any patient complaints.		
Limitations:			
Quality (A/B/C):	C	Applicability (1/2/3):	1

MMSE (0-30) Data Presented Graphically Only

		N	IV Mecobalamin	500 µg 3x/wk	N	N	N Control
Baseline value	**(SD, implied)**	10	20	7			
Final value, 8 wk	**(SD, implied)**	10	21	8			
Post-Tx, 12 wk	**(SD, implied)**	10	20	7			
Difference	**(SE/SD/95% CI)**						
***P* Difference**		*NS (all time points)*					

Mattis' DMR (Japanese Version), Total (0-150) Data Presented Graphically Only

		N	IV Mecobalamin	500 µg 3x/wk	N	N	N Control
Baseline value	**(SD, implied)**	10	112	25			
Final value, 8 wk	**(SD, implied)**	10	115	25			
Post-Tx, 12 wk	**(SD, implied)**	10	115	27			
Difference	**(SE/SD/95% CI)**						
***P* Difference**		*<0.05 (all time points)*					

Outcome(s):	Results (Text) (or Definition)
DMR, sub-scales	Significant increase in Memory ($P<0.05$) No significant change in Attention, Intention & Perseveration, Construction, Conceptualization.
Modified GBS	Significant improvements in Intellectual functions, Emotional functions, and Total ($P<0.05$). No significant change in Initiatives, Different symptoms common in dementia, or Motor function.
Hasegawa's Dementia Rating Scale (HDS)	Significant improvement in scale ($P<0.05$)
Subjective symptoms (insomnia)	Before treatment 6/10 complained of insomnia; all 6 had improvement in sleep.
Neurological symptoms	6/10 had symptoms before treatment. Improvement was seen in 2 who had sensory disturbances. The remaining 4 had no change.
Activities of Daily Living	No significant changes were apparent with treatment.
Caregiver evaluation (list of items)	3/10 improved, 5/10 slightly improved, 2/10 no change. None deteriorated. Items that improved considerably after mecobalamin administration were talkativeness and ability to take initiative.
Overall evaluation (not defined)	3/10 moderately improved, 6/10 slightly improved, 1/10 no change.

Intervention

Author, Year: Ito, 2001	**Ref ID**: 1451	**Vitamins**: B12
Objective: B12 in Alzheimer-type dementia		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Longitudinal, non-randomized one-way partial crossover	Age: 78.3		Alzheimer-type dementia	Physical problems, medication	AD: DSM IV, NINCDS-ADRDA, brain CT
Country:	Japan	%Male: 43%				PD:
Setting:	nd	Race: Japanese				VascDz:
Funding:	nd	Other:				Other:
Comments:	Unclear how those getting Vit B12 were chosen. All received bright light x 4 wk, then half given B12 in addition to bright light. Analysis done on half at 4 wk and on other half with vit B12 + 8 wk bright light					

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Bright light therapy x 8 wk + B12 1.5 mg/d (wk 5-6), B12 3.0 mg/d (wk 7-8)	Bright light therapy x 8 wk	N enrolled:	28	14		14
		N analyzed:	28	14		14
		Drop-outs (%):				
Follow-up duration: 4 wk on B12		Reasons for drop out: No data reported on patients who were not treated with B12				
Comments:						

Primary outcome(s):	Clinical Dementia Rating (Hughes 1982; questionable 0.5 points, mild 1, moderate 2, severe 3), MMSE	
Secondary outcome(s):	Sleep	
Adverse events:	nd	
Limitations:	Analyzed as an uncontrolled cohort	
Quality (A/B/C):	C	Applicability (1/2/3): 2

MMSE		**(0-30)**											
		N	**B12: All**	**1.5-3 mg/d**	**N**	**B12: QMD****	**1.5-3 mg/d**	**N**	**B12: MSD****	**1.5-3 mg/d**	**N**	**Control**	
Baseline value	**(SD)**		nd									nd	
Final value	**(SD)**	14	10.4	7.6							14	10.1	7.3
Difference													
***P* Difference of Final values**		*NS*			*NS*			*NS*					
Baseline value	**(SD)**					nd						nd	
Final value	**(SD)**				6	17.7	5.1				6	17.3	4.5
Difference													
***P* Difference of Final values**					*NS*								
Baseline value	**(SD)**								nd			nd	
Final value	**(SD)**							8	4.9	2.9	8	4.8	2.7
Difference													
***P* Difference of Final values**								*NS*					

* Week 4 of study, when B12 was started

** Subsets: QMD: questionable (0.5 points) or mild (1 point) dementia; MSD: moderate (2 points) or severe (3 points) dementia.

Outcome(s):	**Results (Text) (or Definition)**
Clinical Dementia rating	No change with treatment
Sleep	Significantly less sleep during the day. No difference in sleep at night.

Intervention

Author, Year: Kwok, 1998	**Ref ID**: 354	**Vitamins**: B12
Objective: B12 supplementation of deficient patients on cognitive function		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	RCT	Age:	76.6+/-6.8	77.4+/-6.4	>60 yr and Serum B12 <120 pmol/L, vegetarians living at home or residence (majority of recruits) or non-vegetarians found to be B12 deficient as outpatient (minority of recruits).	Could not cooperate with neuropsychological tests because of severe confusion or communication problems; Hgb <9.0 g/dL, unstable medical condition, signs of combined degeneration of spinal cord	AD:
Country:	Hong Kong	%Male:	4%	0%			PD:
Setting:	Outpatient	Race:	nd	nd			VascDz:
Funding:	nd	Baseline B12 (nmol/L):	87.3+/-24.0	77.9+/-27.8			Dementia: MMSE<20
Comments:	randomization by HK ID card number (odd v even)						

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Cobalamin 1 mg IM x 3 in wk 1, then 1 mg qWk x 3, then 1 mg qMo	No intervention	N enrolled:	nd	nd		nd
		N analyzed:	50	23		27
		Drop-outs (%):				
Follow-up duration: 3-6 months: B12 17.3+/-5.5 wk; Control 16.1+/-3.2 wk		Reasons for drop out:				
Comments: Psychologists were blinded						

Primary outcome(s):	Neuropsychological tests (including motor tests, not included here)		
Secondary outcome(s):			
Adverse events:	nd		
Limitations:	Insufficient data about tests. Mix of 2 different populations.		
Quality (A/B/C):	C	Applicability (1/2/3):	2

Outcome(s):	Definition
MMSE	
Digit span	nd
WAIS-R	Defined as “similarities and block design subtests, and logical memory and visual reproduction subtests”. In Results, listed as Visual and Verbal memory, Verbal and Performance IQ.

WAIS-R, Wechsler Adult Intelligence Scale-Revised

Outcome	**MMSE**	**(0-30)**							
		N	**B12**				**N**	**Control**	
Baseline value	**(SD)**	27	22.2	(4.7)			23	23.8	(4.7)
Final value	**(SD)**	27	22.3	(4.2)			23	24.0	(3.7)
Difference									
***P* Difference**		*NS*					*NS*		
Net Difference									
***P* Net difference**		*NS*							

Outcome	**Visual Memory**	**(nd)**							
		N	**B12**				**N**	**Control**	
Baseline value	**(SD)**	27	12.7	9.0			23	15.3	15.0
Final value	**(SD)**	27	9.7	9.4			23	11.6	12.3
Difference									
***P* Difference**		*NS*					*NS*		
Net Difference									
***P* Net difference**		*NS*							

Outcome	**Verbal Memory**	**(nd)**							
		N	**B12**				**N**	**Control**	
Baseline value	**(SD)**	27	7.8	6.1			23	11.4	6.8
Final value	**(SD)**	27	6.7	5.9			23	9.3	6.2
Difference									
***P* Difference**		*NS*					*<0.05*		
Net Difference									
***P* Net difference**		*NS*							

Outcome	**Digit Span**	**(nd)**							
		N	**B12**				**N**	**Control**	
Baseline value	**(SD)**	27	10.4	3.8			23	11.6	3.5
Final value	**(SD)**	27	10.7	3.6			23	10.6	2.9
Difference									
***P* Difference**		*NS*					*NS*		
Net Difference									
***P* Net difference**		*NS*							

Outcome	**Verbal IQ**		**(nd)**						
		N	**B12**				**N**	**Control**	
Baseline value	**(SD)**	27	58.2	7.1			23	60.1	7.1
Final value	**(SD)**	27	59.3	6.4			23	58.9	7.1
Difference									
***P* Difference**		*NS*					*NS*		
Net Difference									
***P* Net difference**		*NS*							

Outcome	**Performance IQ**		**(nd)**						
		N	**B12**				**N**	**Control**	
Baseline value	**(SD)**	27	74.9*	13.1			23	84.3	15.3
Final value	**(SD)**	27	80.7	12.0			23	85.8	16.7
Difference									
***P* Difference**		*<0.005*					*NS*		
Net Difference									
***P* Net difference**		*NS*							

* Significant difference between intervention and control group at baseline.

When demented patients (n= 7 B12, 3 Control; Diagnosed by psychogeriatrician or MMSE<20), no difference in cognitive test results.

Among the 7 demented subjects who received cobalamin,

1 improved on the MMSE from 18 to 21, digit span, verbal memory, and performance IQ
1 improved on the MMSE from 19 to 24, verbal IQ, and performance IQ
1 improved on the MMSE from 5 to 9, and verbal memory
4 showed no “significant” improvement
None improved on visual memory test.

Intervention

Author, Year:	Lehmann, 2003	**Ref ID**:	1820	**Vitamins**:	B6/B12/Folate
Objective:	Effect of multi-B vitamin on cognition and CSF-tau in mildly cognitively impaired				

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Prospective cohort	Age: 72 (59-81)		Ambulatory, complaining of cognitive disturbances, MMSE 24-30, Serum Hcy >13.5 nmol/L	Serum Cr >120 µmol/L, treatment with a cholinesterase inhibitor	AD:
Country:	Sweden	%Male: 57%				PD:
Setting:	Memory unit	Race: nd				VascDz:
Funding:	Pharmaceutical	Other:				Other:
Comments:						

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Vit B12 1 mg po BID		N enrolled:	30	30		0
Folate 5 mg po BID		N analyzed:	30	30		
Pyridoxine 40 mg po BID		Drop-outs (%):				
Follow-up duration: Mean 270 (110-740) days		Reasons for drop out:				
Comments:						

Primary outcome(s):	MMSE, CSF-tau		
Secondary outcome(s):	CSF Albumin rati:, serum Hcy, B12, folate		
Adverse events:	nd		
Limitations:			
Quality (A/B/C):	C	Applicability (1/2/3):	2

Outcome(s):	**Results (Text) (or Definition)**
MMSE	
CSF-tau	sandwich ELISA with Innotest hTAU-Ag, measuring both normal and hyperphosphorylated tau

Outcome	**MMSE**		**(0-30)**					
		N	**B6/B12/Folate**	**2/10/80 mg**			**N**	**Control**
Baseline value	**(SD)**	30	26.3	(1.8)				
Final value	**(SD)**	30	26.4	(2.4)				
Difference								
***P* Difference**		*NS*						
Net Difference	**(SE/SD/95% CI)**							
***P* Net difference**								

Outcome	**CSF-tau**		**pg/mL**					
		N	**B6/B12/Folate**	**2/10/80 mg**			**N**	**Control**
Baseline value	**(SD)**	30	529	(242)				
Final value	**(SD)**	30	490	(240)				
Difference								
***P* Difference**		*NS*						
Net Difference	**(SE/SD/95% CI)**							
***P* Net difference**								

At baseline CSF-tau was “considerably increased” compared to a non-cognitively impaired control group (222+/-92 pg/mL, n=35).

Intervention

Author, Year:	Martin, 1992	**Ref ID**:	10009	**Vitamins**:	Cobalamin
Objective:	Cognitive effects of cobalamin replacement in patients suffering from cognitive impairment and low serum cobalamin levels				

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Cohort	Age: 79		Consecutive enrollment of cognitive impaired, serum cobalamin < 150 pmol/L	ND	AD:
Country:	USA	%Male: 22				PD:
Setting:	Outpatient geriatric centers, inpt geropsychiatry unit, tertiary care university hospital	Race: ND				VascDz:
Funding:	Government	Other:				Other:
Comments:						

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
1000 mcg cyanocobalamin intramuscular 1 at day for 1 wk, weekly for 1 mo, monthly ≥ 6 mo		N enrolled:	22			
		N analyzed:	18			
		Drop-outs (%):	4			
Follow-up duration:		Reasons for drop out:	Died (2), unable to test due to: dementia (1), deafness (1)			
Comments:	Potential confounders: 3 Pts w/concomitant low serum folate also received oral folate replacement 1 mg @ day, 1 pt on tricyclic antidepressant at start of study, 4 pts on tricyclic antidepressant but was not new change in regimen					

Primary outcome(s):	Changes in DRS scores pre vs post therapy		
Secondary outcome(s):	Comparison of DRS scores by short vs long pretreatment symptom duration		
Adverse events:	nd		
Limitations:			
Quality (A/B/C):	C	Applicability (1/2/3):	1

Outcome(s):	**Definition**
Mattis DRS	Mattis Dementia Rating Scale. Used to evaluate pre & post therapy(≥ 6 mo), pts referred by primary physicians. DRS is 144 point mental status test with following criteria: mild impaired – 120-134, moderately impaired 90-119, severely impaired ≤ 90

Outcome(s):	**Results**
DRS scores	11/18 improved (61%)

Outcome	DRS	Short duration symptoms		Long duration symptoms	
		N	Cobalamin 1000 mcg	**N**	Cobalamin 1000 mcg
Baseline value	(SD)	5	108 (10)	13	108 (19)
Final value	**(SD)**		128 (13)		105 (22)
Difference	**(SE/SD/95% CI)**	P = .0076		P = 0.34	
***P* Difference**					
Net Difference	**(SE/SD/95% CI)**				
***P* Net difference**					
(RR/OR/HR)	**95% CI**				
***P* (RR/OR/HR)**					

Intervention

Author, Year: McGeer, 1972	**Ref ID**: 2107	**Vitamins**: Folic acid
Objective: Effect of folate on PD		

Study characteristics		Population		Controls	Inclusion criteria	Exclusion criteria	Definitions	
Study design	Cohort (design unclear)	Age:	nd		Parkinsonian patients		AD:	
Country:	Canada	%Male:	nd				PD:	nd
Setting:	Clinic	Race:	nd				VascDz:	
Funding:	nd	Other:					Other:	
Comments:								

Intervention(s):	Control:		Total	Intervention 1	Intervention 2	Control
Folic acid 15 mg qD		N enrolled:	nd			
		N analyzed:	18	18		
		Drop-outs (%):				
Follow-up duration: Mean 45 (14-182)		Reasons for drop out:				
Comments:						

Primary outcome(s):	Therapeutic benefit		
Secondary outcome(s):			
Adverse events:	"Only 3 patients reported any adverse effects. One experienced a buzzing in the ears, another a jittery feeling, and a third sleeplessness." No mental changes, weight loss, or gastrointestinal symptoms.		
Limitations:			
Quality (A/B/C):	C	Applicability (1/2/3):	2

Outcome(s):	**Results (Text) (or Definition)**
Therapeutic benefit	6: No therapeutic benefit 11: A slight subjective benefit (without appreciable objective change) 1: Worsening of gait.

Intervention

Author, Year: Meador, 1993	**Ref ID**: 2127	**Vitamins**: B1
Objective: The effect of 3-8 mg/d of thiamine in patients with Alzheimer's disease		

2 Studies

Study 1:

Study characteristics		**Population**		**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	Randomized cross-over	Age:	71 (61-86)	Meeting standard criteria for probable diagnosis of AD. All patients were living with devoted caretaker	h/o alcohol, drug abuse, lab evidence of malnutrition, medications for CNS activity.	AD:	Hachinski score ≤4
Country:	US	%Male:	28%			PD:	
Setting:	Free-living	Race:	nd			VascDz:	
Funding:	Government	Other:				Other:	
Comments:	A double blind placebo controlled cross-over trial with no wash out period						

Intervention(s):	**Control:**		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Thiamine 3 g/d	Placebo	N enrolled:	18	18		18
		N analyzed:		13-17		13-17
		Drop-outs (%):				
Follow-up duration:	1 mo	Reasons for drop out:	ND			
Comments:						

Primary outcome(s):	Mean Alzheimer's Disease Assessment scale score;; Mini-mental status exam
Secondary outcome(s):	Single fiber EMG; The Clinical Global Impression of change (Physician rating of change from baseline)
Adverse events:	No adverse effects were noted
Limitations:	Small N, Poor reporting
Quality (A/B/C): C	Applicability (1/2/3): 2

ADAS	**0-120 (higher score = poorer performance)**						
		N	Thiamine	3g/d	**N**	**Placebo**	
Baseline value	**(SD)**	17	36	25	17	36	25
Final value	**(SD)**	17	41	27	17	44	28
Difference	**(SE/SD/95% CI)**	*+2.1**			*+6.7*		
***P* Difference**		*nd*			*nd*		
Net Difference	**(SE/SD/95% CI)**						
***P* Net difference**		*nd*					

*These numbers are from text. Unclear why they do not correspond to reported data.

MMSE	**0-30**						
		N	Thiamine	3 g/d	**N**	**Control**	
Baseline value	**(SD)**	17	18	7	17	18	7
Final value	**(SD)**	17	18	7	17	17	7
Difference	**(SE/SD/95% CI)**	0			-1		
***P* Difference**		*NS*			*ND*		
Net Difference	**(SE/SD/95% CI)**	+1					
***P* Net difference**		*nd*					

Text:
ADAS scores better in thiamine period than control in 13/17 subjects (P=0.02)
ADAS on thiamine worse than baseline in 9/16 (NS)
ADAS on placebo worse than baseline in 12/16 (P=0.04)
Implicitly 1 patient each scored the same as at baseline during different periods.

MMSE scores were better in thiamine period than control in 6/8 (NS)
MMSE on thiamine worse than baseline in 9/13 (NS)
MMSE on placebo worse than baseline in 11/14 (P=0.03)
Implicitly 9 patients scored the same in both periods and 4 on thiamine and 3 on placebo scored the same as at baseline during different periods.

Study 2:

Study characteristics		Population		Inclusion criteria	Exclusion criteria	Definitions	
Study design	Prospective, longitudinal cohort, with multiple one-way crossovers	Age:	69 (54-93)	Meeting standard criteria for probable diagnosis of AD. All patients were living with devoted caretaker	h/o alcohol, drug abuse, lab evidence of malnutrition, medications for CNS activity.	AD:	Hachinski score ≤4
Country:	US	%Male:	53%			PD:	
Setting:	Free-living	Race:	nd			VascDz:	
Funding:	Government	Other:				Other:	
Comments:	6 of the subjects also participated in the randomized cross-over study, with at least 3.5 months between trials.						

Intervention(s):	Control:		Total	Intervention 1	Intervention 2	Control
Thiamine, 4-6 g	Placebo	N enrolled:	17	17		17
		N analyzed:		14-17*		13-15
		Drop-outs (%):				
Follow-up duration:	1 mo each at 4, 5, 6 g, and placebo	Reasons for drop out:	nd			
Comments:						

* Subsequent phases of trial included 2-13 subjects at "best dose" and between 6.5-8 g

Primary outcome(s):	Mean Alzheimer's Disease Assessment scale score;; Mini-mental status exam
Secondary outcome(s):	Single fiber EMG; The Clinical Global Impression of change (Physician rating of change from baseline)
Adverse events:	All tolerated doses up to 6 g/day well without any side effects. 2 (of 7) subjects reported nausea and indigestion at doses of 7.0 and 7.5 g/day but subsequently tolerated the same dosages in later months.
Limitations:	
Quality (A/B/C): C	Applicability (1/2/3): 2

Phase 1: Open titration, from 4-6 g/day

ADAS	**0-120**	**Month 1**		**Month 4**	
	N	Thiamine	**4 g**	**N**	**Placebo**
Baseline value*	16	27.2		13	26.2
Final value	16	23.4		13	24.1
Difference					
***P* Difference**	*P≤0.01*			*NS*	

ADAS	**0-120**	**Month 2**		**Month 4**	
	N	Thiamine	**5 g**	**N**	**Placebo**
Baseline value*	16	27.2		13	26.2
Final value	16	23.7		13	24.1
Difference					
***P* Difference**	*P≤0.055*			*NS*	

ADAS	**0-120**	**Month 3**		**Month 4**	
	N	Thiamine	**6 g**	**N**	**Placebo**
Baseline value*	16	26.6		13	26.2
Final value	16	24.3		13	24.1
Difference					
***P* Difference**	*NS*			*NS*	

* Baseline means for subjects analyzed in each group.

MMSE	0-30	Month 1		Month 4	
	N	Thiamine	4 g	N	Placebo
Baseline value*	17	21.2		15	21.5
Final value	17	21.7		15	21.9
Difference					
***P* Difference**	*NS*			*NS*	

MMSE	0-30	Month 2		Month 4	
	N	Thiamine	5 g	N	Placebo
Baseline value*	17	21.2		15	21.5
Final value	17	21.8		15	21.9
Difference					
***P* Difference**	*NS*			*NS*	

MMSE	0-30	Month 3		Month 4	
	N	Thiamine	6 g	N	Placebo
Baseline value*	15	21.2		15	21.5
Final value	15	21.7		15	21.9
Difference					
***P* Difference**	*NS*			*NS*	

* Baseline means for subjects analyzed in each group.

Text:
In a month of best dose (month 5) ADAS and MMSE, difference compared to baseline was non-significant (n=13 & 15, respectively).
In months at 6.5 and 7 g/day (months 6,7) ADAS significantly better compared to baseline ($P \leq 0.015$ & $P \leq 0.002$, respectively; n=6).
In months with dose varying from 6.5-8 g/day (months 8, 9, 11, 13) ADAS no different than baseline (n=2-6).
MMSE were unchanged throughout the remainder of the study in 2-7 subjects.

Intervention

Author, Year:	Mimori, 1996	**Ref ID**:	2176	**Vitamins**:	Thiamine
Objective:	To examine the beneficial effect of fursultiamine, in patients using a battery of tests of cognitive function				

Study characteristics		Population		Controls	Inclusion criteria	Exclusion criteria	Definitions	
Study design	Open non-comparative trial	Age:	71.8±6.3		All outpatients who met the DSM-III/R criteria for dementia and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)	ND	AD:	Same as inclusion criteria
Country:	Japan	%Male:	44%				PD:	NA
Setting:	University hospital	Race:	100% Asian				VascDz:	NA
Funding:	Private	Other:	Mean duration of illness: 2.3±1.4 yr				Other:	NA
Comments:	Fursultiamine (thiamine tetrahydrofurfuryl disulfide hydrochloride (TTFD) a derivative of thiamine which is easily converted into the active form of thiamine in the body							

Intervention(s):	Control:		Total	Intervention 1	Intervention 2	Control
Fursultiamine 100 mg/d in 2 divided doses	NA	N enrolled:	9	8	NA	NA
		N analyzed:	9	9		
		Drop-outs (%):	11% (1/9)			
Follow-up duration: 12 wk		Reasons for drop out:	Family commitments			
Comments: 1 patient that did not complete the study was included in the analysis Thiamine measured using HPLC method						

Primary outcome(s):	Hasegawa Dementia Scale (HDS)		Total score 32.5 (**higher score** indicates better performance). Widely used in as screening tests of cognitive function in Japan along with MMSE
Primary outcome(s):	Mini-Mental State Examination (MMSE)		Total score 30 (**higher score** indicates better performance)
Primary outcome(s):	Rating scale by Gottfries (Modified GBS)		Total score 228 (**lower score** indicates better function) Assesses intellectual function, spontaneity, emotional function, motor function, and other symptoms of dementia
Secondary outcome(s):	Blood level of thiamine		
Adverse events:	All patients tolerated the drug and dosages well		
Limitations:	Small sample size		
Quality (A/B/C):	C	Applicability (1/2/3):	1

Outcome(s):	**Results (Text) (or Definition)**
Blood level of thiamine	Baseline Mean blood level of thiamine: 32.5±11.3 (19.5 to 49.3 ng/mL and within normal limits. Among patients with relatively low thiamine levels 1 patient showed some improvement and 1 did not. Blood thiamine levels increased markedly after TTFD administration (257.4±99.4 ng/mL)

HDS Hasegawa Dementia Scale **0-32.5**

		N	Fursultiamine	100 mg/d in 2 divided doses
Baseline value	**(SD)**	9	17.0	(9.7)
Final value	**(SD)**	9	17.6	(10.4)
Difference	**(SD)**	0.6		(0.7)
***P* Difference**		*NS*		
Net Difference	**(SE/SD/95% CI)**			
***P* Net difference**				
(RR/OR/HR)	**95% CI**			
***P* (RR/OR/HR)**				

MMSE	**Mini-Mental State Exam**	**0-30**		
		N	Fursultiamine	100 mg/d in 2 divided doses
Baseline value	**(SD)**	9	17.2	(7.0)
Final value	**(SD)**	9	19.4	(9.0)
Difference	**(SD)**	2.2		(2.0)
***P* Difference**		*<0.05*		
Net Difference	**(SE/SD/95% CI)**			
***P* Net difference**				
(RR/OR/HR)	**95% CI**			
***P* (RR/OR/HR)**				

Total GBS	Gottfries (Modified GBS)	**0-228**		
		N	Fursultiamine	100 mg/d in 2 divided doses
Baseline value	**(SD)**	9	59.8	(38.5)
Final value	**(SD)**	9	52.4	(41.8)
Difference	**(SD)**	-7.4		(3.3)
***P* Difference**		*<0.1(NS)*		
Net Difference	**(SE/SD/95% CI)**			
***P* Net difference**				
(RR/OR/HR)	**95% CI**			
***P* (RR/OR/HR)**				

Intervention

Author, Year:	Mitsuyama, 1988	**Ref ID**:	2185	**Vitamins**:	B12
Objective:	To examine the effect of CH3-B12 on the CNS and clinical effectiveness for organic mental symptoms. To determine the correlation between the serum vitB12 and CSF vitB12				

Study characteristics		Population		Controls	Inclusion criteria	Exclusion criteria	Definitions	
Study design	Non comparative open trial and correlational study	Age:	53±3.1 (34-77)		Subjects who fulfilled the clinical criteria of dementia. Confirmed in all patients by the finding of cerebral atrophy and widening of the ventricles on the CT scan.	Any disorder known to affect vit B12 metabolism, such as acute physical disease, malnutrition, severe anemia, and myeloproliferative disorders and abnormal kidney and liver disorders	AD:	Same as inclusion criteria
Country:	Japan	%Male:	64%				PD:	NA
Setting:	Academic hospital	Race:	100% Asian				VascDz:	NA
Funding:	ND	Other:					Other:	Pick's disease
Comments:	4 patients were mildly demented; 7 moderately demented; 3 patients were severely demented							

Intervention(s):	Control:		Total	Intervention 1	Intervention 2	Control
Vit B12 2mg/d for 60d	None	N enrolled:	14	5	9	
Vit B12 2 mg/d PO and 500μg/d IM		N analyzed:	14	5	9	
		Drop-outs (%):	0			
Follow-up duration: 60 days		Reasons for drop out: NA				
Comments: Sr and CSF B12 assessed by radioassay range between 25 to 1600 pg/mL						

Primary outcome(s):	Change in GBS scale (a neuropsychological scale developed by Gottfries) Correlation between serum and CSF vit B12		
Secondary outcome(s):	Correlation of sr and CSF-VB 12 with severity of dementia		
Adverse events:	ND		
Limitations:	Small sample size (only 1 patient with AD and W-K); 1 patient had unclassified presenile dementia; all mostly had pick's disease		
Quality (A/B/C):	B (comparative trial and small sample size)	Applicability (1/2/3): 2	Broad range of dementia

Outcome(s):	**Results (Text) (or Definition)**
Correlation of Serum and CSF Vit B12 with severity of dementia	No correlation between the concentration of serum and CSF vit B12 levels and severity of dementia without B12 administration
Change in GBS scale	No change in GBS scale with administration of CH3-B12. However patients on both PO and IM reported improvement in mood and social behavioral changes and enhanced self rating of competencies

Intervention

Author, Year: Nilsson, 2000	**Ref ID**: 2338	**Vitamins**: B12
Objective: A study on dementia patients with specific aim to investigate the relation between B12 deficiency, clinical changes and cerebral blood flow		

Study characteristics		Population		Controls	Inclusion criteria	Exclusion criteria	Definitions	
Study design	Non-randomized trial	Age:	79.8 (6.2)	No controls	Patients selected from consecutive admissions to the psychogeriatric department and those with low serum cobalamin level (155 pmol/L) detected during the diagnostic examination were included	Those with acute or unstable physical conditions and recent cerebrovascular accidents	AD: with late onset	NINCDS-ADRDA criteria and classified according to DSM-III-R as mild, moderate or severe
Country:	Sweden	%Male:	50%				PD:	
Setting:	University hospital	Race:	Probably white				VascDz:	Criteria of NINDS-AIREN for vascular dementia with no major strokes
Funding:	Private foundation-Non Industry	Other:					Other:	Mixed and vascular dementia
Comments:								

Intervention(s):	Control:		Total	Intervention 1	Intervention 2	Control
Hydroxycobalamin 1 mg every second day x 10 times and thereafter 1 mg/month	None	N enrolled:	29	24		
		N analyzed:	24	24		
		Drop-outs (%):	ND			
Follow-up duration: 1 month / 1 wk for MMSE		Reasons for drop out:				
Comments: Final data includes both vasc dementia, AD and mixed dementia						

Sr cobalamin determined using radioassay and reference limit 110-650 pmol/L and 155 pmol/L as the lower reference limit for cobalamin

Primary outcome(s):	Clinical improvement; MMSE score improvement; Cerebral blood flow		
Secondary outcome(s):	Hcy, MMA		
Adverse events:	ND		
Limitations:	Includes patients with delirium. Delirium could be secondary to dementia and as due to cobalamin deficiency; consecutive patient enrollment		
Quality (A/B/C):	C	Applicability (1/2/3):	2

Outcome(s):	**Results (Text) (or Definition)**
Clinical improvement	The 15 patients who responded to cobalamin treatment were judged to be demented to about the same degree as before treatment, although behavioral symptoms diminished. The improved group had mild to moderate dementia at baseline
Cerebral blood flow	The improved group of patients (n=15) had a significant higher value compared to baseline after 1 month. The group of patients with no or little clinical improvement showed non significant decrease after 1 month
Regional cerebral blood flow	There was no significant difference in the rCBF pattern between clinically improved and non-improved cases at baseline. The clinically improved patients showed a general flow increase and regional central temporal blood flow increase compared to baseline ($p<0.05$) The non responders to cobalamin treatment showed a flow increase in primarily sensory motor areas after 1 month ($p<0.03$) and more pronounced central lobe rCBF increase after a longer period of treatment than did the clinically improved group
MMSE	Only 10 patients tested at 1 week, 2 AD, 3 mixed AD+vascular (5 vascular). No further extraction performed

Intervention

Author, Year: Nilsson, 2001	**Ref ID**: 2340	**Vitamins**: B12, folate
Objective: To investigate the effect of B12, folate supplementation on cognitive function in elderly patients with demtentia		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	Non-controlled trial	Age:	78.4 ±8.1	N/A	Consecutive patients with symptoms of organic brain disease referred to a University Hospital for Dx examination and Tx	Patients with acute or unstable conditions, with non-organic psychiatric disease, with ongoing Vit substitution	AD:8	See criteria for Other and VascDz
Country:	Sweden	%Male:	42	N/A			PD:	
Setting:	University Hospital outpatients	Race:	ND	N/A			VascDz: 19	Severity of dementia was assessed by DSM III-R
Funding:	Government, non-profit	Other:					Other: Fronto-temporal dementia: 1; mixed AD with VascDz: 1; other specified: 2; non-specified: 2	Clinical Dx based on psychiatric, neurological, physical, and laboratory investigations, psychometric testing, measurement of regional cerebral blood flow (Risberg 1980), EEG, CT or MRI
Comments:								

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
B12 per os 1mg/d	N/A	N enrolled:	33			N/A
Folate per os 5mg/d		N analyzed:	28			N/A
		Drop-outs (%):	5 (15)			
Follow-up duration: 2 mo		Reasons for drop out:	Severely demented patients who could not cooperate in the tests before or after the Tx			
Comments:						

Primary outcome(s):	MMSE, SKT scores, GI		
Secondary outcome(s):			
Adverse events:	ND		
Limitations:	Small sample size (especially for Hcy subgroups)		
Quality (A/B/C):	C	Applicability (1/2/3):	2

Outcome(s):	**Results (Text) (or Definition)**
MMSE	Total score may vary between 0 and 30, with lower scores indicating severe cognitive impairment
SKT	Short cognitive performance test for assessing memory and attention in the sense of info processing speed; consists of 9 subtests (each limited to a max time 60 sec; total score varies between 0 to 27; higher scores indicate more severe cognitive impairment
Global impression of change (GI)	It was made and documented by an experienced clinician according to a standardized clinical assessment and by interviews with relatives and caregivers. The patients were classified as globally improved (GI score=1) following supplementation when clinician and caregivers /relatives reported improvements in alertness, orientation in time and space, recent memory and fewer clinical fluctuations. Patients who did not improve were classified as unchanged (GI score=0) Among patients with normal Hcy 2/11 improved while among patients with increased Hcy 14/17 improved

Patients with normal Hcy

MMSE		Score										
		N	B12	1mg/d	N	Folate	5mg/d	N	(Intervention)	(Dose)	N	Control
Baseline value	**(SE/SD)**	11	21.3	4.9	11	21.3	4.9				N/A	N/A N/A
Final value	**(SE/SD)**	11	20.9	4.7	11	20.9	4.7				N/A	N/A N/A
Difference	**(SE/SD/95% CI)**	-0.4		ND	-0.4		ND				N/A	N/A
***P* Difference**		*NS*			*NS*						N/A	
Net Difference	**(SE/SD/95% CI)**											
***P* Net difference**												
(RR/OR/HR)	**95% CI**											
***P* (RR/OR/HR)**												

Serum B12 and blood folate concentration were determined by immunoassay using purified intrinsic factor and purified folate binding protein (Vit B12/folate kit; Amersham, UK). The reference intervals for B12 are 110-650 pmol/L and for folate 125-500 nmol/L
Unclear whether SD or SE is reported

Patients with increased Hcy

MMSE		Score										
		N	B12	1mg/d	N	folate	5mg/d	N	(Intervention)	(Dose)	N	Control
Baseline value	**(SE/SD)**	17	17.2	8.3	17	17.2	8.3				N/A	N/A N/A
Final value	**(SE/SD)**	17	21.4	4.7	17	21.4	4.7				N/A	N/A N/A
Difference	**(SE/SD/95% CI)**	+4.2		ND	+4.2		ND				N/A	N/A
***P* Difference**		*<0.01*			*<0.01*						N/A	
Net Difference	**(SE/SD/95% CI)**											
***P* Net difference**												
(RR/OR/HR)	**95% CI**											
***P* (RR/OR/HR)**												

Serum B12 and blood folate concentration were determined by immunoassay using purified intrinsic factor and purified folate binding protein (Vit B12/folate kit; Amersham, UK). The reference intervals for B12 are 110-650 pmol/L and for folate 125-500 nmol/L
Unclear whether SD or SE is reported

Patients with normal Hcy

SKT		Score										
		N	B12	1mg/d	N	Folate	5mg/d	N	(Intervention)	(Dose)	N	Control
Baseline value	**(SE/SD)**	11	15.6	4.5	11	15.6	4.5				N/A	N/A N/A
Final value	**(SE/SD)**	11	14.8	4.9	11	14.8	4.9				N/A	N/A N/A
Difference	**(SE/SD/95% CI)**	-0.8		ND	-0.8		ND				N/A	N/A
***P* Difference**		*NS*			*NS*						N/A	
Net Difference	**(SE/SD/95% CI)**											
***P* Net difference**												
(RR/OR/HR)	**95% CI**											
***P* (RR/OR/HR)**												

Serum B12 and blood folate concentration were determined by immunoassay using purified intrinsic factor and purified folate binding protein (Vit B12/folate kit; Amersham, UK). The reference intervals for B12 are 110-650 pmol/L and for folate 125-500 nmol/L
Unclear whether SD or SE is reported

Patients with increased Hcy

SKT		Score										
		N	B12	1mg/d	N	Folate	5mg/d	N	(Intervention)	(Dose)	N	Control
Baseline value	**(SE/SD)**	17	18.5	5.5	17	18.5	5.5				N/A	N/A N/A
Final value	**(SE/SD)**	17	14.6	4. 35	17	14.6	4. 35				N/A	N/A N/A
Difference	**(SE/SD/95% CI)**	-3.9		ND	-3.9		ND				N/A	N/A
***P* Difference**		*<0.01*			*<0.01*						N/A	
Net Difference	**(SE/SD/95% CI)**											
***P* Net difference**												
(RR/OR/HR)	**95% CI**											
***P* (RR/OR/HR)**												

Serum B12 and blood folate concentration were determined by immunoassay using purified intrinsic factor and purified folate binding protein (Vit B12/folate kit; Amersham, UK). The reference intervals for B12 are 110-650 pmol/L and for folate 125-500 nmol/L
Unclear whether SD or SE is reported

Intervention

Author, Year: Nolan, 1991	**Ref ID**: 2360	**Vitamins**: B1
Objective: To determine efficacy of B1 supplementation on cognitive function tests		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	RCT (Double-blind)	Age:	Total (N=15) mean 76.3 Range 59-87	Patients from geriatric Evaluation Service (sub-specialty clinic) who had clinical Dx of probable or possible AD	ND	AD:	Probable or possible AD as defined by the NINCDS-ADRDA criteria (REF 9 in the paper)
Country:	US	%Male:	Total (N=15) 33			PD:	
Setting:	Nursing home and outpatient clinic	Race:	ND ND			VascDz:	
Funding:	Government /non-profit	Other:				Other:	
Comments: Population characteristics are not given separately for the 2 comparative groups							

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
B1 (HCL) as caps of 1g each	Placebo: lactose (Caps of the same appearance, size, and weight as intervention)	N enrolled:	15	ND		
Dose 3g/d (3 capsules)		N analyzed:	10	5		5
		Drop-outs (%):	5 (33)	8 (14)		
Follow-up duration: 12 months		Reasons for drop out:	Poor compliance: 3; health problems unrelated to intervention: 2; 1: protocol violation			
Comments: An additional analysis was performed including 2 patients who had complete data only for 9 mo (Total N: 12; 6 intervention – 6 control)						

Primary outcome(s):	MMSE
Secondary outcome(s):	Verbal fluency, short (15-item) Boston naming test; constructional praxis test; 10-item word list learning test; tests of recall and recognition
Adverse events:	ND
Limitations:	Small sample size; randomization method not described; power calculation not reported; intention-to-treat analysis not accurately applied; relatively high drop-out rate (33%)
Quality (A/B/C): C	Applicability (1/2/3): 1

Outcome(s):	Results (Text) (or Definition)
CERAD	Patients were seen at 3-mo intervals The CERAD (Consortium to Establish a Registry for AD) neuropsychological battery was administered to each patient by the same examiner at each visit, including the baseline visit. This battery includes the instruments referred as primary and secondary outcomes above: Verbal fluency, Short (15-item) Boston naming test, MMSE, Constructional praxis test, 10-item word list learning test, Recall and Recognition tests
Verbal fluency	Verbal learning scores at 12 mo were significantly lower than those at 3 mo and baseline ($p<0.05$). When 12 patients included in analyses (follow-up: 9 mo), the verbal learning scores at 9 mo were significantly lower than those at all other observations ($p<0.05$).
Short (15-item) Boston naming test	Mean naming scores at 12 mo were significantly lower than those at all other observations ($p<0.05$). The mean MMSE scores at 6 mo were significantly lower than those at all earlier observations ($p<0.05$)
MMSE	A 2-way (group x time) repeated ANOVA measures obtained at the 5 clinic visits indicated NS difference between the comparative groups. The mean MMSE score at mo 3, 6, 9, 12 were significantly lower than baseline ($p<0.05$). The mean MMSE scores at 12 mo were significantly lower than those at all other observations ($p<0.05$). The mean MMSE scores at 9 mo were significantly lower than those at all earlier observations ($p<0.05$). When 12 patients included in analyses (follow-up: 9 mo), the mean MMSE scores at 12 mo were significantly lower than those at all other observations ($p<0.05$).
Constructional praxis test	NS difference between groups
10-item word list learning test	Verbal learning scores at 12 mo were significantly lower than those at 3 mo and baseline ($p<0.05$).
Recall test	Delayed recall scores were not formally analyzed, due to floor effects; only 3 /10subjects were ever able to recall more than 1 item from the 10-word lists, and the most frequent score was 0.
Recognition test	Delayed recognition scores between groups, NS.

All Subjects

Outcome	**MMSE**	**ND**									
		N	**B1**	**3g/d**	**N**	**(Intervention)**	**(Dose)**	**N**	**(Intervention)**	**(Dose)**	**N**	**Control**	
Baseline value	**(SE/SD)**	5	16.6	5.73							5	16	5.7
Final value	**(SE/SD)**	5	10.4	9.13							5	14.6	7.09
Difference	**(SE/SD/95% CI)**	-6.2		<0.05							-1.4		<0.05
***P* Difference**		*ND*									*ND*		
Net Difference	**(SE/SD/95% CI)**	-4.8		ND									
***P* Net difference**		*ND*											

Intervention

Author, Year: Rapin, 1988	**Ref ID**: 10015	**Vitamins**: Folate
Objective: Effect of folate treatment on cognitive function		

Study characteristics		Population		Inclusion criteria	Exclusion criteria	Definitions
Study design	Prospective single cohort	Age:	62+/-5	RBC folate<300 ng/mL. "All patients have memory disorders with fatigability and disinterest for life."	Megaloblastic marrow and organic diseases.	AD: nd
Country:	France	%Male:	nd			PD:
Setting:	nd	Race:	nd			VascDz:
Funding:	nd	Other:				Other:
Comments:						

Intervention(s):	Control:		Total	Intervention 1	Intervention 2	Control
Folinic acid, 50 mg/week po	(none)	N enrolled:		nd		
		N analyzed:		38		
		Drop-outs (%):				
Follow-up duration: 120 days		Reasons for drop out:				
Comments:						

Primary outcome(s):	16 scales that are either not defined or poorly defined.		
Other outcome(s):	Depression scale		
Adverse events:	nd		
Limitations:	Very poor reporting		
Quality (A/B/C):	C	Applicability (1/2/3):	2

Outcome(s):	Definition
PRM 4 from Rey	nd
PRM 6 from Rey	analyzes different stages of memorization visuo verbal, learning capacity, immediate and delayed recall
Benton's VRT	evaluates visuo-spatial memory
3 words of Luria	analyzes verbal interferences
Porteus maze	gives an assessment of perception and visuo-spatial organization
Reaction time test, visual	gives an assessment of psychomotor coordination ability
Reaction time test, auditory	gives an assessment of psychomotor coordination ability
Reaction time test, mixed	gives an assessment of psychomotor coordination ability
PRM 7 from Rey	nd
Video coupled object test	measures associative memory
15 words of Rey	Verbal learning tests
Daily activities test	nd
Compound series of Morisby	evaluates logical reasoning
Porteus maze delayed	studies recall of visuo spatial memory
Video coupled object, delayed	no specific definition
Overlapped drawing by Rey	measures perception and ability to discriminate the figures

Results are displayed graphically, measured as % of deficit compared to separately analyzed age-matched healthy individuals.

Outcome(s):	Results
Cognitive tests	There were significant improvements in the following tests: Benton's VRT; Porteus maze; Video coupled object test; Daily activities test; Compound series of Morisby. Other tests showed no difference from baseline to 120 days of treatment.

Intervention

Author, Year: Seal, 2002	**Ref ID**: 10017	**Vitamins**: B12
Objective: B12 supplementation in elderly. Determination of minimum dose to restore normal serum B12		

Study characteristics		Population			Controls	Inclusion criteria	Exclusion criteria	Definitions
Study design	RCT	Age:	82.0	84.9	77.6	Resident in geriatric center or extended care facility, subnormal serum B12 (between 100-150 pmol/L)	None had a previous history of gastric or bowel surgery or symptoms to suggest malabsorption. Known neoplasm, terminal illness, history or diagnosis of malabsorption, pernicious anemia or other anemia, prior B12 or vitamin supplementation.	AD:
Country:	Australia	%Male:	40%	50%	45%			PD:
Setting:	Geriatric center	Race:	nd	nd	nd			VascDz:
Funding:	Hospital	Other:	~1/3 had dementia (not defined); ~1/2 had cerebrovascular or cardiovascular disease					Other:
Comments:	Double blind							

Intervention(s):	Control:		Total	B12 10 µg	B12 50 µg	Control
Vitamin B12 10 µg daily	Placebo	N enrolled:		10	10	11
Vitamin B12 50 µg daily		N analyzed:		9	10	8
		Drop-outs (%):	0			
Follow-up duration:	~4 wk (mean 31 days, range 27-39)	Reasons for drop out:				
Comments:						

Primary outcome(s):	Serum B12		
Secondary outcome(s):	Mini Mental Status Exam (MMSE), folate, homocysteine, hemoglobin, mean corpuscular volume		
Adverse events:	nd		
Limitations:			
Quality (A/B/C):	B	Applicability (1/2/3):	1

Outcome(s):	Results (Text) (or Definition)

(Separate table for each outcome)

Outcome **MMSE** **(0-30)**

		N	B12	10 µg	N	B12	50 µg		N	Placebo	
Baseline value*	**(SD)**	9	15.4	(7.8)	10	19.7	(5.3)		8	19.6	(6.3)
Final value		9			9				8		
Difference	**(SD)**		0	(2.9)		+1	(3.2)			+1.6	(2.1)
***P* Difference**		*NS (0.49)***									
Net Difference	**(SE/SD/95% CI)**										
***P* Net difference**											

* Baseline values not significantly different from each other.
** ANOVA, comparing all 3 groups simultaneously.

Intervention

Author, Year: Sommer, 2003	**Ref ID**: 3063	**Vitamins**: Folic acid
Objective: Folate supplementation for dementia		

Study characteristics		**Population**		**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	RCT	Age:	77 (68-80)	Age ≥65 yr, Dementia (DSM-III R), serum folate 2-5 µg/L, RBC folate 127-452 µg/L, B12>200 ng/L. (Refrained from vitamin supplementation for at least 1 mo prior to study.)	Seizure disorder, major depression or need for antidepressant medication	AD:
Country:	US	%Male:	57%			PD:
Setting:	Community	Race:	nd			VascDz:
Funding:	nd	Other:				Dementia: DSM-III-R
Comments:	Dx: Probable AD, 3; Dementia not otherwise specified, 2; Lewy body dementia, 1; vascular dementia, 1 Baseline MMSE: mean 20.4 (range 14-27)					

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Folic acid 10 mg BID	Placebo	N enrolled:	11	5		6
		N analyzed:	7	4		3
		Drop-outs (%):	36%			
Follow-up duration: 10 wk		Reasons for drop out:	Tx: Dropped out (did not return calls); Cx: Care giver wanted NH care 1, nausea/diarrhea 1, scheduling difficulties 1			
Comments: Double blind, pill counting performed. One of dropouts apparently described in wrong arm.						

Primary outcome(s):	Language:	
	WAIS-R: Pro-rated Verbal IQ	measure of intellectual function
	Boston Naming Test	object-naming, detect difficulties in confrontation naming
	Controlled Oral Word Association Test	verbal fluency
	Memory:	
	Wechsler Memory Scale (WMS):Logical Memory Subtest	short-term vocabulary
	WMS: Associate Learning Subtest	short-term vocabulary
	Speed/Concentration:	
	Trails A and B	visual scanning, conceptual flexibility, motor speed
	Finger Tapping Test	pure motor speed
Secondary outcome(s):		
Adverse events:	"Safe and well-tolerated."	
Limitations:	1/7 subjects with vascular dementia. Very small N. High dropout.	
Quality (A/B/C):	C	Applicability (1/2/3): 1

Outcome(s):	**Results (Text) (or Definition)**
All	The magnitude of change between baseline and second testing was not statistically significant for folic acid and placebo groups. There was a trend for the folic acid group to perform worse than the placebo group on the Associate Learning Subtest ($P<0.08$) and on Trails B ($P<0.08$), which suggest a trend toward a worsening of cognitive abilities secondary to the folic acid supplementation. Specifically, verbal memory and perceptual motor speed may have been negatively affected.

Outcome **WAIS-R: Pro-rated Verbal IQ** **(Normal mean = 100)**

		N	**Folic acid**	**20 mg**			**N**	**Control**	
Baseline value	**(SD)**	4	107.8	(12.8)			3	110.0	(24.9)
Final value	**(SD)**	4	105.3	(16.7)			3	122.5	(10.6)
Difference									
***P* Difference**									
Net Difference									
***P* Net difference**		*0.81*							

Outcome **Boston Naming Test** **(nd range)**

		N	Folic acid	20 mg			N	Control	
Baseline value	**(SD)**	4	40.8	(19.7)			3	42.3	(15.6)
Final value	**(SD)**	4	42.0	(22.7)			3	43.7	(12.4)
Difference									
***P* Difference**									
Net Difference									
***P* Net difference**		*0.86*							

Outcome **Controlled Oral Word Association Test** **(nd range)**

		N	Folic acid	20 mg			N	Control	
Baseline value	**(SD)**	4	29.5	(10.5)			3	36.0	(24.0)
Final value	**(SD)**	4	32.8	(14.9)			3	31.0	(27.7)
Difference									
***P* Difference**									
Net Difference									
***P* Net difference**		*0.48*							

Outcome **Wechsler Memory Scale: Logical Memory Subtest** **(nd range)**

		N	Folic acid	20 mg			N	Control	
Baseline value	**(SD)**	4	4.9	(2.0)			3	4.6	(5.1)
Final value	**(SD)**	4	4.9	(2.5)			3	6.3	(7.3)
Difference									
***P* Difference**									
Net Difference									
***P* Net difference**		*0.28*							

Outcome **Wechsler Memory Scale: Associate Learning Subtest** **(nd range)**

		N	Folic acid	20 mg			N	Control	
Baseline value	**(SD)**	4	16.6	(2.5)			3	11.0	(3.5)
Final value	**(SD)**	4	9.5	(3.0)			3	11.3	(5.3)
Difference									
***P* Difference**									
Net Difference									
***P* Net difference**		*0.08*							

Outcome **Speed/Concentration: Trails A** **(seconds, nd normal)**

		N	Folic acid	20 mg			N	Control	
Baseline value	**(SD)**	4	233.0	(249.3)			3	277.7	(320.5)
Final value	**(SD)**	4	247.8	(256.2)			3	261.0	(296.5)
Difference									
***P* Difference**									
Net Difference									
***P* Net difference**		*0.16*							

Outcome **Speed/Concentration: Trails B** **(seconds, nd normal)**

		N	Folic acid	20 mg			N	Control	
Baseline value	**(SD)**	4	373.0	(263.7)			3	412.0	(227.6)
Final value	**(SD)**	4	393.3	(239.3)			3	257.3	(269.1)
Difference									
***P* Difference**									
Net Difference									
***P* Net difference**		*0.08*							

Outcome **Speed/Concentration: Finger Tapping Test** **(nd range)**

		N	Folic acid	20 mg			N	Control	
Baseline value	**(SD)**	4	38.4	(9.2)			3	32.7	(9.5)
Final value	**(SD)**	4	37.9	(8.8)			3	24.3	(15.1)
Difference									
***P* Difference**									
Net Difference									
***P* Net difference**		*0.56*							

Intervention

Author, Year: Teunisse, 1996	**Ref ID**: 3238	**Vitamins**: B12
Objective: Effect of B12 repletion on dementia		

Study characteristics		**Population**		**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	Prospective longitudinal cohorts	Age:	77.5+/-5.3	Age ≥65 yr, suspected dementia by general practitioner. Diagnosis of dementia by DSM-III-R criteria. Serum B12 <200 pg/L	Previous neurological, neuroradiological examination or extensive diagnostic laboratory investigation for the same complaints. Serious co-morbidity precluding follow-up	AD:	DSM-III-R
Country:	Netherlands	%Male:	42%			PD:	
Setting:	Clinic	Race:	nd			VascDz:	
Funding:	Government	Duration of symptoms:	45+/-32 mo			Dementia:	DSM-III-R CAMDEX
		B12	150 (35-195)				
Comments:	Study also evaluated a "reference group" of subjects with normal B12. This group not treated. Not included here.						

Intervention(s):	Reference:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Cobalamin 1000 µg qD x 5 days, then qMo, or 1000 µg qWk x 5 days, then bi-monthly	No treatment	N enrolled:	108	26		
		N analyzed:		19		
		Drop-outs (%):		27%		
Follow-up duration: Mean+/-SD: 214+/-64 days		Reasons for drop out:	1 not treated as advised, 1 stroke, 2 died, 3 measurements not available. (2 also were not cooperative with CAMCOG).			
Comments: All but 1 of 26 with subnormal B12 fulfilled criteria for possible AD (1 also had cerebral infarctions).						

Primary outcome(s):	Cognitive impairment, disability in ADL, behavioral changes		
Secondary outcome(s):	Caregiver burden		
Adverse events:	nd		
Limitations:			
Quality (A/B/C):	C	Applicability (1/2/3):	2

CAMDEX, Dutch version of the Cambridge Examination for Mental Disorders of the Elderly

Outcome(s):	Definition
CAMCOG	Subscale of CAMDEX, assesses orientation, language, memory, praxis, attention, abstract thinking, perception and calculation (includes MMSE)
IDDD	Interview for Deterioration in Daily living activities in Dementia, caregiver assessment of functioning in the past week; subscales for initiative and performance (assistance necessary)
RMBPC	Revised Memory and Behavioral Problems; 3 subscales for memory, depression (not included here), and disruptive behavior

B12 intervention		**Test**	**Scale**						
		N	**CAMCOG**	**(0-106*)**	**N**	**IDDD-Init**	**(36-0**)**	**N**	**IDDD-Perf**	**(44-0**)**
Baseline value	**SD**	19	64.9	15.7	19	13.8	9.2	19	12.7	9.7
Final value		17			19			19		
Difference* **	**95% CI**	-1.4		-7.4, +4.6	-4.9		-9.4, -0.4	-7.8		-13.3, -2.3
***P* Difference**		*NS*			*<0.05*			*<0.05*		

B12 intervention		**Test**	**Scale**						
		N	**MMSE**	**(0-30*)**	**N**	**RMBPC-Mem**	**(28-0**)**	**N**	**RMBPC-Dis**	**(32-0**)**
Baseline value	**SD**	19	17.5	7.2	19	17.5	5.0	19	4.4	4.6
Final value		17			19			19		
Difference	**95% CI**	-1.8		-3.5, -0.1	-0.4		-3.5, +2.7	-2.6		-4.8, -0.4
***P* Difference**		*<0.05*			*NS*			*<0.05*		

* High score reflects less deterioration
** High score reflects more deterioration
*** Negative scores reflect deterioration, positive scores reflect improvement.

Although not a true comparison to a control, compared to the reference group of 69 patients with dementia with normal serum B12 at baseline (who were not treated), no significant difference in degree of deterioration.

Intervention

Author, Year: van Asselt, 2001	**Ref ID**: 10005	**Vitamins**: B12
Objective: B12 for cognitive function in B12-deficient people		

Study characteristics		**Population**		**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Prospective longitudinal cohort, Single cross-over with placebo	Age:	71* (64-89)	Community-dwelling, "older," plasma B12 ≤150 pmol/L (One subject had an MMSE score of 23)	None had anemia, low serum or RBC folate, myelopathy, history of B12 deficiency, B12 or folate supplementation, severe diseases, or severe cognitive or sensory problems	AD:
Country:	Netherlands	%Male:	44%			PD:
Setting:	Community	Race:	nd			VascDz:
Funding:	Government	Other:				Other:
Comments:						

*Median

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Hydroxycobalamin 1 mg weekly x 4, then monthly x 4 IM	Placebo (water injection, weekly x 4), prior to start of B12 treatment	N enrolled:	16+2*			
		N analyzed:	16	16	16	
		Drop-outs (%):				
Follow-up duration: 1 mo Placebo, then 5 mo B12		Reasons for drop out: *				
Comments:						

* 16 enrolled. 2 dropped out (1 protocol burdensome, 1 died of lung cancer). In their place, 2 other eligible people agreed to participate.

Primary outcome(s):	Biochemical, EEG, and neuropsychological tests		
Secondary outcome(s):			
Adverse events:	nd		
Limitations:			
Quality (A/B/C):	C	Applicability (1/2/3):	2

Outcome(s):	**Definition**
MMSE	nd
WAIS Forward and Backward Digit Span	nd
Verbal Word Learning Test (immediate and delayed recall)	nd
Verbal Fluency	nd
Similarities	nd
Trail Making Test	nd
Rivermead Behavioral Face Recognition Test	nd
(Geriatric Depression Scale)	

Outcome **Verbal Word Learning Test (Delayed recall)** **(nd on range)**

		N	B12				N	Placebo*	
Baseline MEDIAN	**(Range)**	16	6	(1-11)			16	Same	
Final MEDIAN	**(Range)**	16	11	(2-14)			16	7	(0-13)
Difference									
***P* Difference**		*NS*					*NS*		
Net Difference									
***P* Net difference**		*0.03*							

* 1 month prior to B12 treatment

Outcome **Verbal Fluency** **(nd on range)**

		N	B12				N	Placebo*	
Baseline MEDIAN	**(Range)**	16	20	(14-22)			16	Same	
Final MEDIAN	**(Range)**	16	18	(9-22)			16	15	(7-22)
Difference									
***P* Difference**		*NS*					*0.003*		
Net Difference									
***P* Net difference**		*0.004*							

* 1 month prior to B12 treatment

Outcome **Similarities** **(nd on range)**

		N	B12				N	Placebo*	
Baseline MEDIAN	**(Range)**	16	7 (2-10)				16	Same	
Final MEDIAN	**(Range)**	16	7 (2-10)				16	5	(1-10)
Difference									
***P* Difference**		*NS*					*0.04*		
Net Difference									
***P* Net difference**		*0.05*							

* 1 month prior to B12 treatment

Text:
Performance on **MMSE**, Trail Making Test, Rivermead Behavioral Face Recognition Test, and **Digit Span** remained unchanged.

Intervention and Correlation

Author, Year: Bryan, 2002	**Ref ID**: 10004	**Vitamins**: B12, folate, B6
Objective: To investigate the effects of short-term supplementation in healthy women who took either 750 µg of folate, 15 µg of vitamin B12, 75 mg of vitamin B6 or a placebo daily for 35 days		

Study characteristics		**Population**		**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	RCT, double-blind	Age:	74.08±5.75 SD 65-92	Random sample of females from 3 age bands whose names were selected from the Australian Electoral Rolls, which contains 98% of the adult voting population. Healthy women who did not smoke, who were not pregnant or lactating, not taking oral contraceptives or HRT, and not taking any medication likely to affect mental performance or mood. English as a first language, or proficiency in English.	Missing pre- or post-treatment data	AD: ND
Country:	Australia	%Male:	0			PD: ND
Setting:	Population-based	Race:	ND			Vasc Dz: ND
Funding:	Australian Association of Gerontology	Education:	11.48±3.29 yr			Other:
		# of medical conditions:	1.96±1.58			
		# of supplements:	0.59±1.00			
Comments:	This study has 3 age groups of women: younger age, middle-aged, and older women. We focus on older women.					

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
		N enrolled:	Younger: 56 Middle: 80 Older: 75 Total: 221	ND	ND	ND
Folate 750 µg/day		N analyzed:	Total: 211	ND	ND	ND
Vitamin B12 15 µg/day	Placebo capsule	Drop-outs (%):	4.5%			
Vitamin B6 75 mg/day						
Follow-up duration: 5 weeks		Reasons for drop out: Incomplete data				
Comments: Compliance was monitoring by pill counting. The percentage of each treatment group who reported taking more than 95% of the capsules was: folate, 96%; vitamin B12, 93%; vitamin B6, 94% and placebo, 88%						

Primary outcome(s):	Cognitive measures: 1. Speed of processing: Boxes Test, a measure of sensory-motor speed; and the Digit Symbol-Coding and Symbol Search subtests of the Wechsler Adult Intelligence Scale-III (WAIS-III), both measures of perceptual speed. 2. Working memory: Digit Span-Backwards; Letter-Number Sequencing 3. Memory: Rey Auditory-Verbal Learning Test (RAVLT); and 2 measures of incidental recall: recall of symbols from Digit-Symbol-Coding (WAIS-III) and Activity recall. 4. Executive function: Executive function is conceptualized as a higher order cognitive function that controls and integrates other cognitive activities involved in planning and implementing strategies for performance, monitoring performance and using feedback to adjust future responding. Neuropsychological tests sensitive to frontal lobe function were used, including the Stroop Test; the Self-Ordered Pointing Task; Uses for Common Objects; The Trail Making Test; and Ver bal Fluency, comprising Initial Letter Fluency and Excluded Letter Fluency. 5. Verbal ability: Vocabulary (WAIS-III) and Spot-the-Word. Mood measures: Current mood state was assessed using 2 self-report questionnaires that were completed before the cognitive testing sessions: The Center for Epidemiological Studies-Depression Scale (CESD) and The Profile of Mood States Questionnaire (POMS)	
Secondary outcome(s):	Effects of usual dietary intake on cognitive performance: Dietary intake at baseline was assessed using a self-completed, quantified, FFQ based on Baghurst and Record. This form of the FFQ is regularly updated and has been shown to have a high repeatability and consistency with other dietary intake measurement techniques and has demonstrated good reliability compared with urinary and protein measures. The nutrient composition of the food item per unit weight were taken from Australian and British food tables.	
Adverse events:	ND	
Limitations:	Lack of objective measures of B vitamin status, such as RBC levels, at baseline or dose-response relationships over time. Short duration.	
Quality (A/B/C):	B	Applicability (1/2/3): 1

Correlation of dietary usual intake of B vitamins and cognitive performance at baseline (or before supplementation)

Outcome(s):	**Results (Text) (or Definition)**
Cognitive measures: 1. Speed of processing 2. Working memory 3. Memory 4. Executive function 5. Verbal ability	Folate intake affected Boxes performance across age groups ($p<0.05$), with those in the 2nd intake quartile (65.05±12.91) completing significantly more boxes than those in the 3rd (57.67±14.71) and 4th (55.94±16.49). There were no effects of vitamin B12 intake on any other cognitive measure in older adults. There were no effects of vitamin B12 intake on any cognitive measure in older adults. There was an effect of vitamin B6 intake that interacted with age group for the short delay recall of the RAVLT ($p<0.05$), with older age group participants in the 2nd (10.93±2.43) intake quartile recalling more words than those in the 1st (7.40±3.47). There were no effects of vitamin B6 intake on any other cognitive measure in older adults.

*Older participants had relatively better folate, vitamin B12, and vitamin B6 status than younger and middle-aged women, based on the self-reported FFQ

Age group, year	N	Folate TUL 1000 µg RDI 200µg			Vitamin B12 TUL 20 µg RDI 2µg			Vitamin B6 TUL 100 mg RDI 0.8-1.1 mg		
		Range, µg	% < RDI	% < 0.7 RDI	Range, µg	% < RDI	% < 0.7 RDI	Range, µg	% < RDI	% < 0.7 RDI
Younger (20-30)	56	98-668	29.1	12.7	0.37	20.0	9.1	0.7-4.3	3.6	0
Middle (45-55)	80	64-942	21.3	8.8	1-14	12.5	5.0	1.4-5.7	2.5	0
Older (65-92)	75	135-678	4.1	0	0.58-27	8.1	2.7	0.8-3.8	0	0
Total sample	221	64-942	17.2	7.2	0.37-27	12.9	4.8	0.4-5.7	1.9	0

TUL = tolerable upper limit; % < RDI = percentage of participants below the Australian Recommended Daily Intake (RDI); % < 0.7 RDI = percentage of participants below 70% of the Australian RDI

Effects of short-term supplementation of B vitamins on cognitive performance at baseline

Outcome(s):	**Results (Text) (or Definition)**
Cognitive measures: 1. Speed of processing 2. Working memory 3. Memory 4. Executive function 5. Verbal ability	There were significant main effects of age and/or time for many of the cognitive performance in which performance was more positive with increasing age and at time 2 than time 1, reflecting practice and placebo effects. Post hoc comparisons revealed that older age participants in the folate treatment group identified significantly more words than did those in the placebo group. Post hoc comparisons reveal the that participants in the vitamin B6 and placebo groups generated significantly more words than did those in the folate and vitamin B12 treatment group.

Intervention and Correlation

Author, Year: Clarke, 2003	**Ref ID**: 41	**Vitamins**: B12+folate
Objective: To assess the biochemical efficacy of vitamin supplements in people at high risk of dementia		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	RCT 2x2x2 factorial design	Age: 75 (56-89)		Patients who believed they had memory problems; TICS-M score<27; or clinical diagnosis of dementia (DSM IV criteria) and MMSE=12-26 or on therapy for cognitive function (e.g. Donepezil, Metrifonate, Rivastigmine) for at least 3 months	Fronto-temporal dementia; PD; Huntington's disease; normal pressure hydrocephalus; multivitamins (unless only folate<100mg daily); life-threatening disease or cancer; concern about likely compliance; nursing home residents; peptic ulcer or aspirin sensitivity	AD:	
Country:	UK	%Male:				PD:	
Setting:	outpatients	Race:				VascDz:	
Funding:	Industry; government	Other:				Other:	Clinical Dx of dementia (DSM IV criteria) and MMSE=12-26 or mild cognitive impairment defined by symptoms and a modified TICS-M score<27
Comments: Age given only for total patients enrolled; AD: 84 patients; AD+VascDz: 11; VascDz: 3; cognitive impairment: 47; unknown: 4							

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
B12: 1mg	placebo	N enrolled:	149	74		75
+folate: 2 mg		N analyzed:	128	ND		ND
		Drop-outs (%):	21 (14)			
Follow-up duration: 12 weeks		Reasons for drop out: ND				
Comments: Interventions: aspirin vs. placebo; B12+folate vs. placebo; Vitamin E/C vs. placebo; N analyzed for cognitive function tests in each group not given						

Primary outcome(s):	Biochemical endpoints (homocysteine; folate; B12; isoprostane; thromboxane)		
Secondary outcome(s):	Cognitive function scores (MMSE; ADAS-Cog; Bristol Activities of Daily Living Scale)		
Adverse events:	ND		
Limitations:	Sample calculation not explicitly reported and not performed for treatment efficacy on cognitive function; results for treatment efficacy on cognitive function not mentioned as well as N analyzed in each group; reasons for drop-outs not given. ND on gender; race; small sample for each dementia type.		
Quality (A/B/C):	B	Applicability (1/2/3):	2

Outcome(s):	**Results (Text) (or Definition)**
MMSE, ADAS-Cog, ADL	Not significantly altered by treatment (specific results not shown)
Unadjusted Spearman correlation coefficient between baseline cognitive function scores and baseline level of folate*, B12*	Folate /MMSE: r=0.16, p<0.05; Folate /ADAS-Cog: r = - 0.22, p<0.01; Folate /ADL: r = - 0.20, p<0.05 B12 / MMSE: r= - 0.10, NS; B12/ ADAS-Cog: r= - 0.10, NS; B12/ ADL: r= 0.19, p<0.05
Age adjusted Spearman correlation coefficient between baseline cognitive function scores and baseline level of folate*, B12*	Folate /MMSE: r=0.15, NS; Folate /ADAS-Cog: r = - 0.20, p<0.05; Folate /ADL: r = - 0.19, p<0.05 B12 / MMSE: r= - 0. 05, NS; B12/ ADAS-Cog: r= 0.04, NS; B12/ ADL: r= 0.14, NS

* B12 levels determined by a competitive protein binding immunoassay (REF 23 in the paper); folate levels by a microbioogical method using cryopreserved, microtiter plate method (REF 24 in the paper). No data on normal range are given for any of the methods

Intervention and Correlation

Author, Year: Coimbra, 2003	**Ref ID**: 641	**Vitamins**: Riboflavin (Riboflavin, B6, Folate, B12)
Objective: Effect of riboflavin treatment on motor function in PD		

Study characteristics		**Population**	**Controls (Correlation)**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Prospective longitudinal cohort	Age: 67.5	77.5	Sporadic PD (Correlation controls: Dementia without stroke and a low Mini-Mental score)	(Stroke, ischemic brain lesions)	AD:
Country:	Brazil	%Male: 42%	50%			PD: "Current criteria" (Fahn & Przedborski 2000)
Setting:	Neurology clinic outpatients	Race: nd	nd			VascDz:
Funding:	nd	Other: Hoehn & Yahr Stages: 1, 2, 3 – 10% each; 4 – 26%; 5 – 45%				Other:
Comments:						

Intervention:

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Riboflavin 30 mg TID	None	N enrolled:	31	31		0
(eliminate all red meat from diets)		N analyzed:	19	19		0
		Drop-outs (%):	39%			
Follow-up duration: 6 mo		Reasons for drop out:	Failure to comply for 6 mo			
Comments:						

Primary outcome(s):	Motor capacity	Motor function scale based on expanded version of Hoehn & Yahr scale, with categories of 0 (Requires assistance to stand even on symptomatic drugs for PD), 14, 30, 50 (Unassisted basic care and reduced unsteadiness while on symptomatic drugs for PD), 65, 80 (Bilateral rigidity/tremor + midline changes with normal balance prior to the early morning symptomatic drugs for PD; continuous but reduced symptoms while on symptomatic drugs for PD), 90, 95, 100 (Fully asymptomatic without symptomatic drugs for PD)
Secondary outcome(s):	Reported symptoms	
Adverse events:	nd	
Limitations:	High dropout rate. Completers analysis only. No control. May be confounded by elimination of red meat from diet.	
Quality (A/B/C):	C	Applicability (1/2/3): 2

Outcome(s):	Results (Text) (or Definition)
Reported symptoms	"About 10-15 days after beginning treatment, PD patients often reported better (progressively less interrupted) sleep at night, improved reasoning, higher motivation, and reduced depression. Their family members usually started noticing motor improvements after 20 days of treatment, but in some cases of advanced disability the patient was able to change body position in bed at night as early as on the third day of treatment."

Outcome **Motor Capacity** **(scale 0-100%)** **3 Months**

		N	Riboflavin	30 mg TID	N (Intervention) (Dose)	N (Intervention) (Dose)	N Control
Baseline value	**(SE/SD)**	19	44	nd			
Final value	**(SE/SD)**	19	66	nd			
Difference	**(SE/SD/95% CI)**						
***P* Difference**		*<0.001*					
Net Difference	**(SE/SD/95% CI)**						
***P* Net difference**							

Outcome **Motor Capacity** **(scale 0-100%)** **6 Months**

		N	Riboflavin	30 mg TID	N (Intervention) (Dose)	N (Intervention) (Dose)	N Control
Baseline value	**(SE/SD)**	19	44	nd			
Final value	**(SE/SD)**	19	71	nd			
Difference	**(SE/SD/95% CI)**						
***P* Difference**		*<0.001*					
Net Difference	**(SE/SD/95% CI)**						
***P* Net difference**							

Correlation (Baseline)

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		Total	Population of interest	Control
Plasma Riboflavin*	ng/mL	PD v Dementia without stroke		N enrolled:	41	31	10
Plasma Vitamin B6**	ng/mL			N analyzed:	41	31	10
Plasma Folate***	ng/mL						
Serum Vitamin B12****	pg/mL			Drop-outs (%):			
Comments:							

* Flavin-adenin dinucleotide, HPLC/fluorometric detection, per Speek AJ 1982. ND on normal range.
** Per Sharma SK 1992. ND on normal range.
*** HPLC/microbiological assay, per Kelly P 1996. ND on normal range.
**** Roche Diganostics, electrochemiluminescence immunoassay. ND on normal range.

Other predictors/outcomes reported: Hcy	
Follow-up duration (if applicable):	
Reasons for drop out (if applicable):	
Limitations:	
Quality (A/B/C):	Applicability (1/2/3):

Correlation of Predictors with Outcomes (Baseline)

Description of (Sub-) Groups	Outcome	N	Plasma Riboflavin ng/mL		Plasma B6 nmol/L		Plasma Folate ng/mL		Serum B12 pg/mL	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
PD		31	100.9	22.0	25.3	6.1	5.6	4.0	356.0	261.0
Dementia w/o Stroke		10	128.8	25.6	24.3	9.4	4.3	2.8	440.7	322.5
	P difference		*<0.01*		*NS*		*NS*		*NS*	

Intervention and Correlation

Author, Year: Kral, 1970	**Ref ID**: 1694	**Vitamins**: B12, folate
Objective: To determine the correlation of vit B12 and folic acid levels with the degree of memory impairment and whether parenteral administration of vit B12 would improve their memory function		

Study characteristics		**Population**			**Controls for RCT**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
			XS-1	**RCT-2**				
Study design	XS-part 1 CT-part2	Age:	77	nd	nd	Geriatric ward and homes for the aged in the Montreal area	Subacute combined degeneration, sensory deficiencies; aphasia; those on vitamins, anticonvulsants, chemotherapy, blood transfusions	AD: nd
Country:	Canada	%Male:	59%	39%	55%			PD: nd
Setting:	University and community	Race:	nd	nd	nd			VascDz: nd
Funding:	Gov	Other:						Other: nd
Comments:	Part 1 correlation: 12 without psychological or neurological symptoms; 9 senile dementia; 24 cerebral arteriosclerosis; 18 diagnosis undetermined Part 2 was Intervention: 18 formed the experimental group; 22 the control group							

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Vit B12 x 5times/wk x 14 wk	No treatment	N enrolled:	Part 1: 63			
			Part 2: 40	18		22
		N analyzed:	Part 1: 53			
			Part 2: 40	18		22
		Drop-outs (%):	nd			
Follow-up duration: 14 wk		Reasons for drop out: nd				
Comments: Vit B12 <200 μmg/ml; folic acid <4 μmg/ml were considered as vitamin deficient						

Sr vit B12 measured by microbiological assay according to the method of Ross using Euglena gracilis
Sr folic acid was determined by the method of Baker using Lactobacillus casei in a microbiological assay

Primary outcome(s):	Part 1: correlation of vitamins with memory impairment	Part 2: Comparison of change in memory quotient between treatment and control groups
Secondary outcome(s):	weight	
Adverse events:	ND	
Limitations:	Results presents as text only; 53 analyzed not randomized; but single blinded study	
Quality (A/B/C):	C	Applicability (1/2/3): 1

Memory function was measured by the standard **Wechsler Memory Scale**. The upper and lower limit of retention span was done using counting test (Cameron 1943)

Outcome(s):	**Results (Text) (or Definition)**
Memory quotient	The correlation study did not reveal any significant correlation between the level of serum vit B12 or folic acid and any measure of senile impairment in the population as a whole. The same analysis performed separately for each sex it was found that in women the serum vit B12 level was positively correlated within MQ at the 0.1 level of significance
Treatment effect	No significant change of the MQ was observed in either the vit B12 deficient subgroup, or in the subgroup with folate def as a result of treatment In the subgroup with combined def, the MQ of the 2 experimental subjects increased minimally, whereas the mean MQ of the two experimental subjects dropped sig after the treatment

Number of subjects	MQ >100	80-100	60-80	<60
Average Sr B12 μμmg/ml	294	409	304	153
Average Sr folate μmg/ml	5.20	4.00	6.96	8.30
Ratio Folate/B12	1:56	1:100	1:42	1:18
B12 to folate ratio did not correlate with MQ, but correlated positive at the 0.01 level of significance with the senile score on the age relevant check list				

Memory Quotient	**(0-100)**					
		N	**Vit B12 5x/wk**	**7000 mg (total)**	**N**	**Control**
Baseline value	**(ND)**	18	90		22	88
Final value	**(ND)**	18	87		22	92
Difference	**(ND)**		-3			+4
***P* Difference**		*NS*				
Net Difference						
***P* Net difference**		*NS*				

Lower limit of retention span	**ND**					
		N	**Vit B12 5x/wk**	**7000 mg (total)**	**N**	**Control**
Baseline value	**(ND)**	18	38		22	45
Final value	**(ND)**	18	26		22	27
Difference	**(ND)**		-12			+4
***P* Difference**		*NS*			*NS*	
Net Difference						
***P* Net difference**		*NS*				

Upper limit of retention span	**ND**					
		N	**Vit B12 5x/wk**	**7000 mg (total)**	**N**	**Control**
Baseline value	**(ND)**	18	48		22	45
Final value	**(ND)**	18	42		22	72
Difference	**(ND)**		-6			-5
***P* Difference**		*NS*			*NS*	
Net Difference						
***P* Net difference**		*NS*				

Correlation and Intervention

Author, Year: Lewerin, 2005	**Ref ID**: 10002	**Vitamins**: B12/Folate/B6
Objective: Multi-B vitamin for cognitive and movement in general population elderly		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	RCT	Age:	75.7 +\-4.7	75.6 +\-4.0	Community dwelling men and women who underwent cognitive testing and Postural-Locomotor-Manual testing		AD:
Country:	Sweden	%Male:	38%	44%			PD:
Setting:	Community	Race:	nd	nd			VascDz:
Funding:	Private	Other:					Other:
Comments:							

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Cyanocobalamin 500 µg/day	Placebo	N enrolled:	195	126		69
Folate 800 µg/day		N analyzed:		105-115		57-64
Vit B6 HCl 3 mg/day		Drop-outs (%):				
Follow-up duration: 4 mo		Reasons for drop out:	Illness, difficulty/pain, refusal, poor compliance (7), other			
Comments: Tests performed at different visits. Different numbers evaluated for different tests.						

RCT:

Primary outcome(s):	Cognitive and Postural-Locomotor-Manual tests		
Secondary outcome(s):			
Adverse events:	nd		
Limitations:			
Quality (A/B/C):	B	Applicability (1/2/3):	3

Outcome(s):	Definition
Postural-Locomotor-Manual testing (movement time)	Opto-electronic technique to evaluate time to lift, carry, and deposit an object
Simultaneity index	Overlap time of different phases (sum of times of 3 individual phases/total time)
Digit span forward and backward	Short term memory
Identical forms	Perceptual speed (time to marking identical form)
Visual reproduction	Visual memory (ability to remember and draw 4 forms)
Synonyms	Verbal ability (finding synonyms)
Block design	Spatial ability (reproduce design with colored blocks)
Digit symbol	Perceptual speed (time to replace digits with symbols by a code)
Thurstone's Picture Memory Test	Long term memory (ability to remember pictures)
Figure classification	Inductive reasoning (ability to choose figure different from others)

Baseline Correlation:

Predictor(s): (eg, B vit level)		Outcome(s): Definition:		Total	Population of interest	Control
Plasma Folate*	nmol/L	Movement time	N enrolled:	209	All evaluated together	N/A
Whole blood Folate**	nmol/L	Simultaneity index	N analyzed:	195-207		
Serum Vit B12***	pmol/L	Block design	Drop-outs (%):			
(Serum MMA	µmol/L)	Digit symbol				
(Plasma Homocysteine	µmol/L)					
Comments:	14 subjects were excluded from RCT prior to start of RCT because of "difficulty/pain".					

MMA, methylmalonic acid
* Diagnostic Products Corp, Solid Phase No Boil Dualcount. Normal range: 6–35 nmol/L.
** Diagnostic Products Corp, Solid Phase No Boil Dualcount. Normal range: 100–450 nmol/L.
*** Diagnostic Products Corp, Solid Phase No Boil Dualcount. Normal range: 130–750 pmol /L.

Correlation of Predictors with Outcomes (Baseline): Multivariate analysis*

Description of (Sub-) Groups	N	Plasma Folate nmol/L					Whole blood Folate nmol/L					Serum B12 pmol/L				
		Mean	SD	β	R^2	*P*	Mean	SD	β	R^2	*P*	Mean	SD	β	R^2	*P*
All: Block Design (WAIS)	207	16.0	6.61	+0.029	0.13	NS	351	134.9	-0031	0.13	NS	325	159.3	+0.0028	0.13	NS

All: Digit Symbol (WAIS)	204	+0.083 0.10 NS	-0.004 0.10 NS	+0.0038 0.10 NS

β, Regression coefficient
* Adjusted for age, sex, smoking, serum creatinine

Digit Span Forward (WAIS) **(0-9)**

		N	B vitamins				N	Control	
Baseline value	**(SD)**	115	5.8	1.1			64	5.9	1.2
Final value		115					64		
Difference	**(SEM)**	+0.24		0.09			+0.33		0.14
***P* Difference**									
Net Difference									
***P* Net difference**		*NS*							

Digit Span Backward (WAIS) **(0-8)**

		N	B vitamins				N	Control	
Baseline value	**(SD)**	115	4.4	1.2			64	4.6	1.0
Final value		115					64		
Difference	**(SEM)**	+0.25		0.09			+0.22		0.16
***P* Difference**									
Net Difference									
***P* Net difference**		*NS*							

Identical Forms **(0-60)**

		N	B vitamins				N	Control	
Baseline value	**(SD)**	115	23.3	7.6			61	24.8	8.1
Final value		115					61		
Difference	**(SEM)**	+0.13		0.37			+1.5		0.56
***P* Difference**									
Net Difference									
***P* Net difference**		*0.04**							

* Note placebo better than B vitamins

Visual Reproduction (0-14)

		N	B vitamins			N	Control	
Baseline value	**(SD)**	113	6.9	3.1		62	7.0	3.0
Final value		113				62		
Difference	**(SEM)**	+0.61		0.23		+0.6		0.28
***P* Difference**								
Net Difference								
***P* Net difference**		*NS*						

Synonyms (0-30)

		N	B vitamins			N	Control	
Baseline value	**(SD)**	110	22.5	4.7		61	22.4	5.0
Final value		110				61		
Difference	**(SEM)**	+0.31		0.25		+1.3		0.3
***P* Difference**								
Net Difference								
***P* Net difference**		*0.02**						

* Note placebo better than B vitamins

Block Design (WAIS) (0-42)

		N	B vitamins			N	Control	
Baseline value	**(SD)**	114	18.5	6.3		61	20.0	7.7
Final value		114				61		
Difference	**(SEM)**	+0.99		0.37		+0.80		0.50
***P* Difference**								
Net Difference								
***P* Net difference**		*NS*						

Digit Symbol (WAIS) **(0-90)**

		N	B vitamins				N	Control	
Baseline value	**(SD)**	113	35.1	10.0			62	38.0	12.1
Final value		113					62		
Difference	**(SEM)**	+0.95		0.52			+2.31		0.51
***P* Difference**									
Net Difference									
***P* Net difference**		*0.09**							

* Note placebo better than B vitamins

Thurstone's Picture Memory Test **(0-28)**

		N	B vitamins				N	Control	
Baseline value	**(SD)**	115	20.3	4.8			63	21.1	3.9
Final value		115					63		
Difference	**(SEM)**	+1.75		0.30			+2.41		0.42
***P* Difference**									
Net Difference									
***P* Net difference**		*NS*							

Figure Classification **(0-30)**

		N	B vitamins				N	Control	
Baseline value	**(SD)**	113	15.8	4.8			62	16.8	4.9
Final value		113					62		
Difference	**(SEM)**	+1.45		0.33			+0.60		0.55
***P* Difference**									
Net Difference									
***P* Net difference**		*NS*							

Neither basal Hcy, MMA, B12, folate showed associations with change in cognitive performance.

Intervention and Correlation

Author, Year:	Mitsuyama, 1988	**Ref ID**:	2185	**Vitamins**:	B12
Objective:	To examine the effect of CH3-B12 on the CNS and clinical effectiveness for organic mental symptoms. To determine the correlation between the serum vitB12 and CSF vitB12				

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	Non comparative open trial and correlational study	Age:	53±3.1 (34-77)		Subjects who fulfilled the clinical criteria of dementia. Confirmed in all patients by the finding of cerebral atrophy and widening of the ventricles on the CT scan.	Any disorder known to affect vit B12 metabolism, such as acute physical disease, malnutrition, severe anemia, and myeloproliferative disorders and abnormal kidney and liver disorders	AD:	Same as inclusion criteria
Country:	Japan	%Male:	64%				PD:	NA
Setting:	Academic hospital	Race:	100% Asian				VascDz:	NA
Funding:	ND	Other:					Other:	Pick's disease
Comments:	4 patients were mildly demented; 7 moderately demented; 3 patients were severely demented							

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Vit B12 2mg/d for 60d	None	N enrolled:	14	5	9	
Vit B12 2 mg/d PO and 500μg/d IM		N analyzed:	14	5	9	
		Drop-outs (%):	0			
Follow-up duration: 60 days		Reasons for drop out: NA				
Comments: Sr and CSF B12 assessed by radioassay range between 25 to 1600 pg/mL						

Primary outcome(s):	Change in GBS scale (a neuropsychological scale developed by Gottfries) Correlation between serum and CSF vit B12		
Secondary outcome(s):	Correlation of sr and CSF-VB 12 with severity of dementia		
Adverse events:	ND		
Limitations:	Small sample size (only 1 patient with AD and W-K); 1 patient had unclassified presenile dementia; all mostly had pick's disease		
Quality (A/B/C):	B (comparative trial and small sample size)	Applicability (1/2/3): 2	Broad range of dementia

Outcome(s):	**Results (Text) (or Definition)**
Correlation of Serum and CSF Vit B12 with severity of dementia	No correlation between the concentration of serum and CSF vit B12 levels and severity of dementia without B12 administration
Change in GBS scale	No change in GBS scale with administration of CH3-B12. However patients on both PO and IM reported improvement in mood and social behavioral changes and enhanced self rating of competencies

Intervention and Correlation

Author, Year: Shaw	**Ref ID**: 2954	**Vitamins**: Folate, B12
Objective: Effect of B12/Folate on cognitive function in patients with AD and low folate		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Randomized Xover	Age:	80.6+/-6.7		In-patients diagnosed with senile dementia. RBC folate <130 ng/mL	Serious impairment of cardiac, pulmonary or renal function. Cerebral arteriosclerosis	AD:
Country:	UK	%Male:	nd				PD:
Setting:	In-patients	Race:	nd				VascDz:
Funding:	nd	Other:					Other:
Comments:	Double blind. No washout.						

Intervention(s):	Control:		**Total**	**Intervention 1**	**Intervention 2**	**Control**
Hydroxycobalamin 1000 µg IM x 7 days, then weekly Folate 15 mg po daily	Placebos	N enrolled:	66	66		66
		N analyzed:	17	17 (10 first arm)		17 (7 first arm)
		Drop-outs (%):	74%			
Follow-up duration: 12 wk		Reasons for drop out:	"Patients selected were severely demented and many had difficulty in cooperating sufficiently" on testing			
Comments:						

Primary outcome(s):	Psychometry (see tests below)		
Secondary outcome(s):	Folate, B12, other levels		
Adverse events:	nd		
Limitations:	Inappropriate tests used for such severely demented group. Thus ¾ dropouts. Data incomplete.		
Quality (A/B/C):	C	Applicability (1/2/3):	1

Outcome(s):	**Definition**
Synonym Learning Test	
Digit Copying Score	Kendrick 1967
Dementia Scale (without Changes in Personality)	
Information-Memory-Concentration Test	Blessed 1968

Intervention

The means for the Dementia Scales were unchanged in both groups. Those for The Information-Memory-Concentration scores rose slightly, but the increment was not statistically significant.

Correlation

Author, Year: Andersen-Ranberg, 2001	**Ref ID**: 119	**Vitamins**: B12, Folate
Objective: Relation of dementia to other diseases		

Study characteristics		**Population**		**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	100	Cases:	Cases:	AD:	
	Comparative	%Male:	22%	All individuals in Denmark turning 100 y.o. between 4/1/95 and 5/31/96.	Refused (n=56). Died within weeks of birthday, prior to contact (n=13). Missing data (n=11).		
	Prospective	Race:	nd			PD:	
Country:	Denmark	Other:		Controls:	Controls:	VascDz:	
Setting:	Population					Dementia:	WHO (1992) ICD-10. Severity rated by Clinical Dementia Rating (CDR; Hughes et al, 1982)
Funding:	Government						
Comments:							

Predictor(s): (eg, B vit level)	Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
"B12 or Folate deficiency"	Demented	ICD-10	N eligible:	276		
			N analyzed:	196	105	91
			Drop-outs (%):			
Comments:						

Other predictors/outcomes reported:	CVD, DM, Hypothyroid, PD		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):	See Exclusion criteria		
Limitations:	Limited details or analyses. Centenarians only.		
Quality (A/B/C): C		Applicability (1/2/3):	1

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Serum B12 or Folate deficiency (nd) *p*				
		n	%			
Demented	105	9	9%	nd		
Non-demented	91	10	11%			

Correlation

Author, Year: Anello, 2004	**Ref ID**: 123	**Vitamins**: Folate, B12
Objective: MTHFR polymorphisms and AD		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age:	71.0+/-6.6	69.5+/-12.7	Cases:	Cases:	AD: CERAD
	Comparative	%Male:	nd	nd	Ambulatory, AD		
	Prospective	Race:	nd	nd			PD:
Country:	Italy	Raiseberg score >6:	30%		Controls:	Controls:	VascDz:
Setting:	Clinic	Early onset (<65 y) AD:	23%		Ambulatory, from same geographical area	AD	Other:
Funding:	nd						
Comments:							

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Vitamin B12*	pmol/L	AD Diagnosis		N enrolled:	361	180	181
Folates*	nmol/L	Dementia severity	Reisberg scale (1982)	N analyzed:	361	180	181
Homocysteine	µmol/L	Age of AD onset	Early: <65 y				
ApoE ε4							
MTHFR				Drop-outs (%):			
Comments:							

* Abbott IMX automated Benchtop analyzer system, Microparticle enzyme immunoassay (MEIA). No data on normal range.

Other predictors/outcomes reported:	Transcobalamin gene (TCN1)		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:			
Quality (A/B/C):	B	Applicability (1/2/3):	2

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Plasma B12 pmol/L		p	Plasma Folates nmol/L		p	(Sr/CSF) (B vit) (unit)			(Sr/CSF) (B vit) (unit)			p
		Mean	SD		Mean	SD		Mean	SE/SD	r=	Mean	SE/SD	r=	
AD	180	278	221	NS	14.3	5.7	0.09							
Controls	181	283	211		15.7	5.9								

Logistic Regression Predictors:	N	Diagnosis of AD						
		OR (Unadjusted)		P (univariate)	P (multivariate*)			
Folate	361	0.95	(0.91, 1.00)	0.04	NS (0.2)			
Vitamin B12		1.00	(0.99, 1.01)	NS	NS			

* Adjusted for MTHFR, ApoE ε4, and TCN1 genotypes, and homocysteine level (and other B vitamin)

Outcome(s):	Results (Text)
Severity of dementia (Reisberg scale)	"Plasma levels of (Hcy,) folate and vitamin B12 were not influenced by the severity of dementia or age of onset of the disease."

Correlation

Author, Year: Argyriadou, 2001	**Ref ID**: 144	**Vitamins**: B12, Folate
Objective: Association between cognitive impairment and anemia		

Study characteristics		**Population**		**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age:	65-74: 50% 75-84: 35% 85+: 15%	Cases: Age ≥65 y a. living in geriatric facility (n=48), b. visit geriatric community center (n=75), c. received routine care at health center (n=413)	Cases:	AD:
	Non-comparative	%Male:	46%			
	Prospective	Race:	nd			PD:
Country:	Greece	Other:		Controls:	Controls:	VascDz:
Setting:	Community					Possible cognitive impairment: MMSE≤24
Funding:	nd (report no conflicting interests)					
Comments:						

Predictor(s): (eg, B vit level)		Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
Vitamin B12 (normal v abnormal)*	Abnl: <145 pg/mL	MMSE	N enrolled:		536	
Folate (normal v abnormal)*	Abnl: <1.8 ng/mL		N analyzed:		536	
			Drop-outs (%):			
Comments:						

* Micro Merieux analyzer, ELISA.
** Imx automatic analyzer, Ion Capture Immune Assay (ICIA).

Other predictors/outcomes reported:	Hematocrit, Age		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Limited analyses. Potentially biased sample due to eligibility criteria		
Quality (A/B/C):	C	Applicability (1/2/3):	3

Outcome(s):	Results (Text)

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N (Total)	%	*p*	N (Men)	%	*p*	N (Women)	%	*p*
Normal B12 (≥145 pg/mL)									
MMSE ≤24	480	37.9%		221	34.8%		259	40.5%	
MMSE >24		62.1%			65.2%			59.5%	
Low B12 (<145 pg/mL)									
MMSE ≤24	56	55.4%	nd	24	62.5%	0.008	32	50%	NS
MMSE >24		44.6%			37.5%			50%	
Normal Folate (≥1.8 ng/mL)									
MMSE ≤24	521	39.5%		239	37.7%		282	41.1%	
MMSE >24		60.3%			62.3%			58.9%	
Low Folate (<1.8 ng/mL)									
MMSE ≤24	15	46.7%	NS	6	33.3%		9	55.6%	
MMSE >24		53.3%		66.7%	66.7%			44.4%	

Logistic Regression Predictors:	N	MMSE ≤24					
		OR (Adjusted*)		*P* (multivariate)			
Low B12 (<145 pg/mL)	536	2.0	(1.1, 4.0)	0.03			
Low Folate (<1.8 ng/mL)		3.8	(0.9, 15.2)	0.06			

* Adjusted for age, intake site, and presence of anemia (and other B vitamin)

Correlation

Author, Year: Assantachai, 1997	**Ref ID**: 157	**Vitamins**: B1, B12, Folate
Objective: Association of B1, B12, and folate deficiency and cognitive impairment		

Study characteristics		**Population**			**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	69.3	(60-87)	Cases:	Cases:	AD:	
	Non-comparative	%Male:	39%		Enrolled in geriatric day centers,			
	Prospective	Race:	Thai		independently living, "well living".		PD:	
Country:	Thailand	TMSE:	27.38	(2.02)	Controls:	Controls:	VascDz:	
Setting:	Community (rural)						Cognitive impairment:	TMSE<24
Funding:	nd							
Comments:								

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Thiamin pyrophosphate effect (normal: 0-15%)*	%	Thai Mental State Examination (TMSE)*	6 categories (orientation, registration, attention, calculation, language, abstract thinking, recall) Maximum 30	N enrolled:		203	
Vitamin B12**	pg/mL			N analyzed:			
RBC Folate***	ng/mL			Drop-outs (%):			
Comments:							

* Spectrophotometry. No data on normal range.
** Radiodiolution assay (Co^{57}). No data on normal range.
*** Microbioassay using lactobacillus casei ATCC 7469 and spectrophotometry. No data on normal range.

Other predictors/outcomes reported:			
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:			
Quality (A/B/C):	B	Applicability (1/2/3):	3

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	Serum B1 effect (%)				Serum B12 (pg/mL)				RBC Folate (ng/mL)			
	N	Mean	SD	*P*	N	Mean	SD	*P*	N	Mean	SD	*P*
Cognitively impaired (TMSE<24)	63	12.44	8.81	NS	51	460	488	NS	44	416	123	NS
Normal (TMSE≥24)	138	10.90	7.68		108	408	184		103	399	143	

Correlation

Author, Year: Bernard, 1998	**Ref ID**: 269	**Vitamins**: B12
Objective: Association of B12 (different measurements) and cognitive impairment		

Study characteristics		**Population**			**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age:	71.5	(65-89)	Cases:	Cases:	AD:
	Non-comparative	%Male:	99%		Ambulatory veterans, age≥65 y, who came to outpatient laboratory		
	Prospective	Race:	White*	88%			PD:
			Black	9%			
			Other	3%			
Country:	US	Other:			Controls:	Controls:	VascDz:
Setting:	Community (VA)						Other:
Funding:	Government						
Comments:							

* Non-Hispanic

Predictor(s): (eg, B vit level)		Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
B12 deficiency	< laboratory norm (200 pg/mL)*	MMSE	N enrolled:		303	
B12 deficiency	< laboratory norm (200 pg/mL)* or >200 & <300 pg/mL & either MMA >2 SD above normal (271) or Hcy >2 SD above normal (16)		N analyzed:		303	
			Drop-outs (%):			
Comments:						

* No data on measurement method.

Other predictors/outcomes reported:	RAND 36-Item Health Survey		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:			
Quality (A/B/C):	B	Applicability (1/2/3):	2

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	MMSE (0-30)		*p*	BDS		
		Mean*	SD		Mean		
B12 <200 pg/mL	19	22.54	1.89	<0.05	4.19		
B12 ≥200 pg/mL	284	27.21	2.02		4.07		
					4.17		
B12 deficient (broad)**	49	26.78	2.04	NS (0.15)	4.00		
B12 normal (broad)	254	27.25	2.01				

*Least Squares mean (adjusted for alcohol intake (yes/no), vitamin use, annual income (dichotomous at $10,000), level of education.
** < laboratory norm (200 pg/mL) or (>200 & <300 pg/mL & either MMA >271 or Hcy >16)

Correlation

Author, Year: Bowirrat, 2002	**Ref ID**: 395	**Vitamins**: B12, Folate
Objective: Evaluation of dissociation between AD and ApoE ε4 in population of Arabs		

Study characteristics		**Population**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Longitudinal	Age:	Cases:	Cases:	AD: DSM-IV
	Non-comparative	%Male:	Age ≥60 y, resident in 3 Arab villages in northern Israel	Refused to participate (n=12)	PD:
	Prospective	Race: Arab	Controls:	Controls:	VascDz:
Country:	Israel	Other:			Other:
Setting:	Community (rural)				
Funding:	Government, Private non-profit, Industry				
Comments:					

Predictor(s): (eg, B vit level)	Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Plasma B12*	Dementia of the Alzheimer type (DAT)	DSM-IV	N surveyed:	823		
Plasma Folate*	Incident (new onset) DAT		N analyzed:	234	76	158
Comments:						

* No data on methodology used or normal range.

Other predictors/outcomes reported:	ApoE ε4, age, concomitant medical conditions, smoking		
Follow-up duration (if applicable):	Mean 20+/-4 (up to 23.4) months		
Reasons for drop out (if applicable):	Labwork drawn only from 234/823 subjects		
Limitations:	No results data reported, "perhaps the lowest ApoE ε4 frequency reported in the world: 3.5% Cx, 4.5% AD)		
Quality (A/B/C):	C	Applicability (1/2/3):	3

Outcome(s):	Results (Text)
Baseline AD prevalence	Plasma B12 and plasma folate levels did not differ significantly between AD patients and controls after adjusting for year of birth.
AD incidence	Subjects (in the highest Hcy tertile or) in the lowest B12 and folate tertile did not have greater risk to develop AD after adjustment for year of birth and gender.

Correlation

Author, Year: Bunce, 2004	**Ref ID**: 444	**Vitamins**: B12, Folate
Objective: Association of ApoE ε4 and B12/Folate with cognitive impairment		

Study characteristics		**Population**		**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age: 82.8	(5.7)	Cases: Age ≥75 y,	Cases: Dementia, depression, incomplete laboratory data, B12 or folate supplementation, "abnormally high" folate levels	AD: DSM-III-R
	Non-comparative	%Male: 20%				
	Prospective	Race: nd				PD:
Country:	Sweden	Other:		Controls:	Controls:	VascDz:
Setting:	Community					Other:
Funding:	Government, Private non-profit					
Comments:						

Predictor(s): (eg, B vit level)		Outcome(s):			**Total**	**Population of interest**	**Control**
Serum B12*	pmol/L	Free recall of sematically unrelated words	2 lists of 12 concrete nouns, presented slowly or rapidly, immediate recall	N potential from survey:		528	
Serum Folate*	nmol/L	Free and cued recall of organizable words	23 nouns belonging to categories, presented slowly	N analyzed:		167	
ApoE genotype							
Comments:							

* Radioimmunoassay. No data on normal range.

Other predictors/outcomes reported	
Follow-up duration (if applicable):	
Reasons for drop out (if applicable): See Exclusions	
Limitations: Multiple exclusions and missing data	
Quality (A/B/C): B	Applicability (1/2/3): 2

* Multiple detailed ANOVA and ANCOVA results were reported.

Correlation

Author, Year: Bunce, 2005	**Ref ID**: 445	**Vitamins**: B12, Folate
Objective: Association of B vitamin with cognition, correlation with ApoE genotype		

Study characteristics		**Population**		**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age:	82.8	Cases: ≥75 y	Cases: Dementia, clinical depression, incomplete B12 or folate data, B12 or folate supplement, abnormally high folate, ApoE data unavailable	Dementia:: DSM III-R
	Non-comparative	%Male:	20%			
	Prospective	Race:	~100% white			PD:
Country:	Sweden	Other:	8.9 yr education			VascDz:
Setting:	Community					Other:
Funding:	Private and Government					
Comments:	Excluded people with dementia					

Predictor(s): (eg, B vit level)		Outcome(s):			**Total**	**Population of interest**	**Control**
Serum B12*	Low: <251 pmol/L	Face recognition:	20 famous faces from 1930-1950 & 20 contemporary 1980s	N enrolled:	167	Non-demented	none
Serum Folate*	Low: <13 nmol/L	Short term memory	WAIS-R forward and backward digit span (FDS, BDS)	N analyzed:	167		
ApoE genotype	ε4 vs non-ε4	Visuospatial ability	WAIS-R Block design test, Clock setting and reading ability	Drop-outs (%):	(361 did not meet criteria, including 150 with incomplete data and 32 with elevated folate level)		
Comments:							

* Radioimmunoassay

Other predictors/outcomes reported	none
Follow-up duration (if applicable):	NA
Reasons for drop out (if applicable):	NA
Limitations:	Excluded people with dementia, Did not analyze B vitamins as continuous variables.
Quality (A/B/C): B	Applicability (1/2/3): 3

Outcome(s):	Results (Text)
Recognition of contemporary and dated famous faces B12 and ApoE	Low B12 (<251 pmol/L) significantly associated with poorer face recognition scores (p=0.008). Two-way interaction of B12 and ApoE (ε4 vs non-ε4) non-significant
Visuospatial skills B12 and ApoE	No significant associations for Clock reading, or Clock drawing
Recognition of contemporary and dated famous faces Folate and ApoE	Low Folate (<13 nmol/L) significantly associated with poorer face recognition scores (p=0.011). Two-way interaction of Folate and ApoE (ε4 vs non-ε4) non-significant
Visuospatial skills Folate and ApoE	No significant associations for Clock reading, or Clock drawing

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	**N**	**FDS (0-9)**		***p***	**BDS (0-9)**		***p***	**Block Design (0-42)**		***p***	
		Mean	**SD**		**Mean**	**SD**		**Mean**	**SD**		
ApoE ε4 Normal B12	21	5.52	1.29		4.19	1.03		13.95	4.53		
ApoE ε4 Low B12 (<251 pmol/L)	28	5.36	0.91	NS*	4.07	0.94	NS*	12.32	4.30	NS*	
ApoE non-ε4 Normal B12	64	5.83	1.15		4.17	1.11		14.95	5.55		
ApoE non-ε4 Low B12 (<251 pmol/L)	54	5.26	1.09		4.00	1.06		11.33	5.72		
ApoE ε4 Normal Folate	34	5.47	1.21		4.00	0.92		13.56	3.83		
ApoE ε4 Low Folate (<13 nmol/L)	15	5.33	0.72	NS*	4.40	1.06	NS*	11.80	5.51	NS*	
ApoE non-ε4 Normal Folate	88	5.57	1.10		4.15	1.07		13.56	5.88		
ApoE non-ε4 Low Folate (<13 nmol/L)	30	5.57	1.10		3.93	1.14		12.79	5.93		

FDS, WAIS-R forward digit span; BDS, WAIS-R backward digit span;
* NS by ANCOVA adjusted for age, years of education, gender, stroke, coronary heart disease, other heart disease and diabetes, and cerebrovascular disease.

Correlation

Author, Year: Cacabelos, 2004	**Ref ID**: 477	**Vitamins**: B12, Folate
Objective: Comparison of AD and vascular dementia		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	71	70	Cases: Diagnosed with AD by conventional criteria. MMSE<24 and Hachinski<6	Cases:	AD:	DSM-IV, NINCDS-ADRDA, ICD-10
	Comparative	%Male:	36%	45%			PD:	
	Prospective	Race:	nd	nd				
Country:	Spain	Other:			Controls:	Controls:	Vascular dementia	NINDS-AIREN
Setting:	nd				Diagnosed with dementia with vascular component, including vascular dementia, mixed dementia, and patients with cerebrovascular disorders, MMSE<24, Hachinski>6		Cerebrovascular disorders:	Stroke, cardiogenic and/or hypertensive vascular encephalopathy, chronic cerebrovascular insufficiency
Funding:	nd							
Comments:	Source of subjects unclear							

Predictor(s): (eg, B vit level)		Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
Folate (blood)*	ng/mL	Dx AD	N enrolled:			
Vitamin B12 (blood)**	pg/mL		N analyzed:	939	465	474
Interaction with ApoE genotype	2/3 v 2/4 v 3/3 v 3/4 v 4/4		Drop-outs (%):			
Comments:						

* No data on measurement technique. Folate deficiency defined as folate < 3.0 ng/mL.
** No data on measurement technique. B12 deficiency defined as B12 < 150 pg/mL.

Other predictors/outcomes reported:	107 laboratory, radiographic, history, physical examination variables, genomics		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations: No correction for multiple testing or adjustments made			
Quality (A/B/C):	B	Applicability (1/2/3): (no data on source of sample)	2

Outcome(s):	Results (Text)
Folate interaction with ApoE genotype	No significant difference in folate levels between patients with AD and specific ApoE genotypes and their counterparts with vascular dementia.
B12 interaction with ApoE genotype	Patients with AD and ApoE 2/4 (n=4 or 6) had significantly lower B12 level (364+/-141 pg/mL) than patients with vascular dementia and ApoE 2/4 (n=9; 678+/-365 pg/mL; *P*<0.04). AD patients with other genotypes had similar B12 levels as their counterparts with vascular dementia.

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	**N**	**Blood Folate ng/mL**			***p***	**Blood B12 pg/mL**			***p***		
		Mean	**SD**	**Deficiency***		**Mean**	**SD**	**Deficiency****			
AD	465	6.10	2.81	5%	NS (mean)	487.95	327.83	4%	NS (mean)		
Vascular dementia	474	6.31	3.13	6%		520.98	504.80	3%			

* < 3.0 ng/mL
** <150 pg/mL

Correlation

Author, Year: Clarke, 1998	**Ref ID**: 622	**Vitamins**: Folate, B12
Objective: Hcy (Folate, B12, MTHFR) and AD		

Study characteristics		**Population**			**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS (with autopsy in some) Longitudinal	Age*:	All 73.2+/-8.6	Autopsy 76.6+/-8.0	72.8+/-8.8	Cases: Cognitive dysfunction, referred to Oxford Project to Investigate Memory and Ageing. Histologically confirmed at autopsy (n=76) or clinical diagnosis of probable or possible AD (n=88)	Cases: Age <55 y, no blood sample available	AD: Histology at autopsy (CERAD criteria) or NINDS-ADRDA
	Comparative	%Male:	39%	37%	43%			
	Retrospective	Race:	nd	nd	nd			
Country:	UK	CAMCOG:	55.2	45.1	97.8	Controls: Elderly volunteer controls without symptoms of memory impairment (17 of whom were patients' relatives)	Controls:	
Setting:	Clinic	MMSE	16.2	12.8	28.5			
Funding:	Pharmaceutical							
Comments:	Subset of subjects analyzed by Refsum 2003 Ref ID 2661							

* Age at time of laboratory testing, regardless of when diagnosis made (ie, autopsy)
CAMCOG, Cambridge Cognitive Examination, maximum score 107
MMSE, Mini-Mental Status Examination, maximum score 30

Predictor(s): (eg, B vit level)		Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
Serum Folate*	nmol/L	AD vs non-AD	N enrolled:	272	164	108
RBC Folate*	nmol/L	Medial temporal lobe CT	N analyzed:	272	164	108
Serum B12**	pmol/L					
(Serum Hcy	µmol/L)					
(ApoE ε4 allele	frequency)					
(MTHFR homozygous mutant	frequency)		Drop-outs (%):			
Comments:						

* Microbiological assay. No data on normal range.
** Radioimmunoassay. No data on normal range.

Other predictors/outcomes reported:	
Follow-up duration (if applicable):	XS and 4 years
Reasons for drop out (if applicable):	

Limitations:	
Quality (A/B/C): B	Applicability (1/2/3): 2

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Serum Folate nmol/L		p	RBC Folate nmol/L		p	Serum B12 Pmol/L			
		Mean	SD	r=	Mean	SD	r=	Mean	SD	r=	
AD (all)	164	17.6	10.7	<0.001	866	446	<0.05	236	112	NS	
AD (subset w/histology)	76	15.2	9.5	<0.001	737	386	<0.001	215	79	<0.05	
Healthy controls	108	22.9	10.0	--	991	407	--	253	100	--	

Description of (Sub-) Groups	N	Clinically Diagnosed AD				N	Histologically confirmed AD			
		OR (Adj 1*)		OR (Adj 2*)			OR (Adj 1*)		OR (Adj 2*)	
Serum Folate >24.2 nmol/L	272	1		1		184	1		1	
Serum Folate 17.2-24.2 nmol/L		0.8	(0.5-1.4)	0.7	(0.4-1.5)		0.6	(0.2-1.6)	0.4	(0.1-1.5)
Serum Folate <17.2 nmol/L		2.5	(1.7-3.8)	2.3	(1.4-3.8)		5.0	(3.1-8.2)	3.3	(1.8-6.3)
Serum B12 >280 pmol/L	272	1		1		184	1		1	
Serum B12 200-280 pmol/L		1.3	(0.8-2.0)	1.7	(1.0-3.0)		2.1	(1.2-3.6)	5.6	(2.6-11.9)
Serum B12 <200 pmol/L		1.4	(0.9-2.2)	1.4	(0.8-2.5)		1.8	(1.0-3.2)	4.3	(2.1-8.8)
									OR (Adj 2+Hcy**)	
Serum Folate <17.2 nmol/L									1.6	(0.8-3.2)
Serum B12 <200 pmol/L									2.2	(0.8-5.2)

* Adj 1, adjusted for age and sex; Adj 2, adjusted for age, sex, smoking, social class, and ApoE ε4.
** Addition of Hcy to multivariate model

Outcome(s):	Results (Text)
AD Diagnosis	60% of patients with DAT and 76% with histologically confirmed AD had serum folate concentrations in the bottom 1/3 of the control distribution
Longitudinal CT scan of age-corrected minimum thickness of the Medial Temporal Lobes (annual x 4 yr)	Non-significant trend toward association between both serum folate and B12 at first visit and disease progression, as assessed by thinning medial temporal lobes

Correlation

Author, Year: Crystal, 1994	**Ref ID**: 695	**Vitamins**: B12
Objective: Longitudinal association between low B12 and cognitive dysfunction		

Study characteristics		**Population**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Longitudinal	Age: (75-85)	Cases:	Cases:	AD: DSM-III, NINCDS-ADRDA
	Non-comparative	%Male: nd	Age 75-85 y, residing in the community, healthy, cognitively intact.		PD:
	Prospective	Race: nd			
Country:	US	Other:	Controls:	Controls:	VascDz:
Setting:	Community				Other:
Funding:	Government				
Comments:					

Predictor(s): (eg, B vit level)	Outcome(s):	Definition:		**Total**	**Population of interest**	
Serum Vitamin B12* pg/mL	Fuld Object Memory Evaluation (FOME)	test of recent memory	N enrolled:		nd	
	Blessed Test of Information, Memory and Concentration (BIMC)		N analyzed:		410	
			Drop-outs (%):			
Comments:						

* Corning RIA: Normal geometric mean 458 (95% CI 171, 953) pg/mL

Other predictors/outcomes reported:			
Follow-up duration (if applicable):	5 years		
Reasons for drop out (if applicable):			
Limitations:	Incomplete description of study sample, tests, or results		
Quality (A/B/C):	C	Applicability (1/2/3):	3

Outcome(s):	Results (Text)

Correlation of Predictors with Outcomes (Baseline)

Description of (Sub-) Groups	N	FOME (nd)		p	BIMC (nd)		p		
		Mean	r=		Mean	r=			
Serum Vit B12 <150 pg/mL	22	7.10	0.01	NS	2.23	-0.03	NS		
Serum Vit B12 >150 pg/mL	388	7.40			2.46				

Correlation of Predictors with Outcomes (At time of diagnosis of AD vs. Baseline all)

Description of (Sub-) Groups	N	Serum B12 pg/mL	p			
		Mean				
AD (time of diagnosis)	19	551	NS			
Cognitively intact (baseline, all subjects)	410	558				

Correlation of Predictors with Outcomes (Longitudinal)

Description of (Sub-) Groups	N	AD**		p	All Dementia**		p		
		n	%		n	%			
Serum Vit B12 <150 pg/mL (baseline)*	22	3	4.5%	NS	1	13.6%	NS		
Serum Vit B12 >150 pg/mL (baseline)	388	29	7.5%		57	14.7%			

* Treated by private physicians for B12 deficiency.
** Incidence over 5 years.

Correlation

Author, Year: Duthie, 2002	**Ref ID**: 10003	**Vitamins**: Folate and B12
Objective: The potential contributions of blood Vit B12, folate, and Hcy concentrations to individual differences in life cognitive variance after taking childhood IQ into account		

Study characteristics		**Population ABC 21**	**ABC 36**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS/Longitudinal	Age: 77	62	Cases: Invited to participate the 2 cohorts of survivors of Aberdeen 1921 Birth cohort and Aberdeen 1936 Birth cohort in 2 assessments during the years 1998-1999(wave 1) and the second in 1999-2000 (wave 2)	Cases: Blood b12 conc was 664 pmol/L and blood folate >59nmol/L	AD:
	Comparative	%Male: 50%	ND			
	Retrospective	Race: Probably white	Probably white			PD:
Country:	UK	Other:		Controls:	Controls:	VascDz:
Setting:	Academic setting					Other: Dementia <24 suggestive of mild dementia <20 indicate dementia
Funding:	Private non industry and Gov					
Comments:	2 cohorts with different birth yrs ie survivors of Aberdeen 1921 Birth cohort and Aberdeen 1936 Birth cohort were used for the study					

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest ABC21**	**ABC36**
Vit B12	pmol/L	MMSE	<24 suggestive of mild dementia <20 indicate dementia	N enrolled:	335	186	148
Folate	nmol/L			N analyzed:	309	165	144
				Drop-outs (%):	1%		
Comments:							

Plasma and RBC folate and vit B12 were measured using Simultrac Radioassay kit vit B12 ^{57}Co/folic acid ^{125}I

Other predictors/outcomes reported:	Predictors: National adult reading test (NART); Ravens progressive matrices (RPM); Auditory verbal learning test (AVLT); Block design (BD); Digital symbol subtest (DS) Outcomes: Homocysteine		
Follow-up duration (if applicable):	ND		
Reasons for drop out (if applicable):	3 patients were removed from the analysis because their blood level for vitamins met the exclusion criteria		
Limitations:			
Quality (A/B/C):	B	Applicability (1/2/3):	3

Correlation of Predictors with Outcomes (cross-sectional studies) (MMSE vs vit)

Description of (Sub-) Groups	N	Sr	B 12	pmol/L	*p*	Pl	Folate	nmol/L	*p*	RBC	Folate	µg/g protein	*p*	(Sr/CSF)	(B vit)	(unit)	*p*
		Mean	CI	r=		Mean	CI	r=		Mean	CI	r=		Mean	SE/SD	r=	
ABC21	165	280.0	263.5, 296.1	0.24	<0.01	16.8	15.6, 17.9	0.20	<0.05	1.04	0.98, 1.1	0.13	NS				
ABC36	144	291.5	275.9, 296.1	0.03	NS	17.7	16.3, 19.0	0.0	NS	0.98	0.92, 1.04	-0.03	NS				

Correlation of Predictors with Outcomes (cross-sectional studies)* (MMSE vs vit)

Description of (Sub-) Groups	N	Sr	B 12	pmol/L	*p*	Pl	Folate	nmol/L	*p*	RBC	Folate	µg/g protein	*p*	(Sr/CSF)	(B vit)	(unit)	*p*
		Mean	CI	r=		Mean	CI	r=		Mean	CI	r=		Mean	SE/SD	r=	
ABC21	165	280.0	263.5, 296.1	+0.23	<0.01	16.8	15.6, 17.9	0.19	<0.05	1.04	0.98, 1.1	0.09	NS				
ABC36	144	291.5	275.9, 296.1	+0.05	NS	17.7	16.3, 19.0	0.02	NS	0.98	0.92, 1.04	-0.046	NS				

* adjusted for childhood intelligence quotient

Correlation of Predictors with Outcomes (cross-sectional studies) (BD vs vit)

Description of (Sub-) Groups	N	Sr	B 12	pmol/L	*p*	Pl	Folate	nmol/L	*p*	RBC	Folate	µg/g protein	*p*	(Sr/CSF)	(B vit)	(unit)	*p*
		Mean	CI	r=		Mean	CI	r=		Mean	CI	r=		Mean	SE/SD	r=	
ABC21	165	280.0	263.5, 296.1	-0.06	NS	16.8	15.6, 17.9	+0.06	NS	1.04	0.98, 1.1	0.02	NS				
ABC36	144	291.5	275.9, 296.1	+0.03	NS	17.7	16.3, 19.0	0.24	<0.05	0.98	0.92, 1.04	0.08	NS				

Correlation of Predictors with Outcomes (cross-sectional studies)* (BD vs vit)

Description of (Sub-) Groups	N	Sr	B 12	pmol/L	*p*	Pl	Folate	nmol/L	*p*	RBC	Folate	µg/g protein	*p*	(Sr/CSF)	(B vit)	(unit)	*p*
		Mean	CI	r=		Mean	CI	r=		Mean	CI	r=		Mean	SE/SD	r=	
ABC21	165	280.0	263.5, 296.1	-0.07	NS	16.8	15.6, 17.9	0.07	NS	1.04	0.98, 1.1	0.01	NS				
ABC36	144	291.5	275.9, 296.1	0.097	NS	17.7	16.3, 19.0	0.24	<0.01	0.98	0.92, 1.04	0.19	NS				

* adjusted for childhood intelligence quotient

Correlation of Predictors with Outcomes (cross-sectional studies) (DS vs vit)

Description of (Sub-) Groups	N	Sr	B 12	pmol/L	*p*	Pl	Folate	nmol/L	*p*	RBC	Folate	µg/g protein	*p*	(Sr/CSF)	(B vit)	(unit)	*p*
		Mean	CI	r=		Mean	CI	r=		Mean	CI	r=		Mean	SE/SD	r=	
ABC21	165	280.0	263.5, 296.1	0.03	NS	16.8	15.6, 17.9	0.19	<0.05	1.04	0.98, 1.1	0.19	<0.05				
ABC36	144	291.5	275.9, 296.1	0.10	NS	17.7	16.3, 19.0	0.14	NS	0.98	0.92, 1.04	0.08	NS				

Correlation of Predictors with Outcomes (cross-sectional studies)* (DS vs vit)

Description of (Sub-) Groups	N	Sr	B 12	pmol/L	*p*	Pl	Folate	nmol/L	*p*	RBC	Folate	µg/g protein	*p*	(Sr/CSF)	(B vit)	(unit)	*p*
		Mean	CI	r=		Mean	CI	r=		Mean	CI	r=		Mean	SE/SD	r=	
ABC21	165	280.0	263.5, 296.1	-0.03	NS	16.8	15.6, 17.9	0.19	<0.05	1.04	0.98, 1.1	0.09	NS				
ABC36	144	291.5	275.9, 296.1	0.159	NS	17.7	16.3, 19.0	0.111	NS	0.98	0.92, 1.04	0.03	NS				

* adjusted for childhood intelligence quotient

Correlation

Author, Year: Engelborghs, 2004	**Ref ID**: 918	**Vitamins**: B12, folate
Objective: To test for possible correlations of decreased sr vit B12 and red cell folate levels with degree of cognitive impairment and extent of behavioral and psychological signs and symptoms of dementia among AD and FTD patients		

Study characteristics		**Population**			**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	79±7	69±11	Cases: Consecutively hospitalized patients for diagnostic work up of dementia	Cases: Patients on vitamin supplementation, alcohol abuse, and artificially fed	AD:	Based on NINCDS-ADRDA criteria and DSM-IV
	Comparative	%Male:	48%	50%				
	Prospective	Race:	ND	ND			PD:	
Country:	Belgium	Other:Disease duration	4±3	6±4 P=<0.001	Controls: Same as above	Controls: Same as above	VascDz:	
Setting:	Academic hospital	MMSE score	12.7±6.9	16.3±8.3 P=0.02			Other: FTD	MMSE, Hierarchic dementia scale,global deterioration scale
Funding:	University and private non-industry							
Comments:	Staging of dementia done on global deterioration scale							

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**	**Control (FTD)**
Sr vit B12	193-982 pg/mL	Hierarchic Dementia scale	0-10	N enrolled:	180	152	28
Red cell folate	93-641 ng/mL	MMSE	0-30	N analyzed:	180	152	28
				Drop-outs (%):	0		
Comments:	Vit B12 and folate assessed by use of solid phase radioassay kits						

Other predictors/outcomes reported:	Behavioral testing (Behave AD; cohen Mansfield Agitation; verbally agitated behavior; cornell scale for depression)		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Compared to fronto temporal dementia and only significant correlations available		
Quality (A/B/C):	C	Applicability (1/2/3):	2

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Sr B 12 vit pg/mL			*p*	Red cell Folate ng/mL			*p*
		Mean	SD	r=		Mean	SE/SD	r=	
AD-HDS	152	382.8	257.8	ND	NS	245.5	197.5	0.205	0.03
FTD-HDS	28	316.6	120.0	0.538	0.014	277.2	195.2	ND	NS
AD-MMSE	152			ND	NS			ND	NS
FTD-MMSE	28			ND	NS			0.443	0.02

Correlation

Author, Year: Garcia, 2004	**Ref ID**: 1063	**Vitamins**: B12, Folate
Objective: Association with cognitive function in elderly		

Study characteristics		**Population**			**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age:	73.0	(4.9)	Cases: Age ≥65 y, Independent-living, attend senior community center	Cases: Oral B12 >37.5 µg/day, Parenteral B12, history of ileal/gastric surgery, Serum Creatinine >130 mmol/L, neurological disease (eg, dementia, stroke, severe head trauma, PD), depression, MMSE<24, hospitalization within prior 3 months, any acute medical condition	AD:
	Non-comparative	%Male:	25%				
	Prospective	Race:	nd				PD:
Country:	Canada	MMSE:	28.3	(1.52)	Controls:	Controls:	VascDz:
Setting:	Community						Other:
Funding:	Private non-profit						
Comments:							

Predictor(s): (eg, B vit level)	Outcome(s):	Definition:		**Total**	**Population of interest**
Serum pmol/L Vit B12*	Mattis DRS	screening for dementia, includes subtests for attention, initiation, perseveration, construction, conceptualization, and memory	N enrolled:	281	281
(RBC nmol/L) Folate**	Stroop Neuropsychological Screening Inventory		N analyzed:	281	281
	California Verbal Learning Test (CVLT)	Verbal learning characteristics in 5 categories: recall measures, learning characteristics, recall errors, recognition measures, and contrast measures. Each metric analyzed separately. Appears that for each outcome, the metric that was most strongly correlated was marked as "Factor 1" and analyzed alone. Each outcome thus analyzed against different metrics of the CVLT.			
			Drop-outs (%):		
Comments:					

* Standard radioimmunoassay. Normal range 165-740 pmol/L
** Standard radioimmunoassay. Normal range 200-1300 nmol/L. Measured, but no analyses reported.

Other predictors/outcomes reported:	Methylcitric acid, MMA, Hcy		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Analyses opaque		
Quality (A/B/C):	C	Applicability (1/2/3):	2

Outcome(s):	Results (Text)
CVLT	Analysis unclear and very difficult to interpret. Authors conclude that Vitamin B12 levels did not significantly correlate after multivariate analysis with the psychometric measures

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Stroop (Max 112)			*p*	Mattis (Max 144)			*p*		
		Mean	SD	r=		Mean	SD	r=			
Low Vit B12	44	83.4	21.4		NS	138.8	4.7		NS		
Normal Vit B12	237	82.7	18.8			139.0	4.2				

Correlation

Author, Year: Gold, 1995	**Ref ID**: 1119	**Vitamins**: Thiamine
Objective: Thiamine levels among patients at memory clinic		

Study characteristics		**Population***	**Controls****	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age: 77.8+/-7.7	74.9+/-6.4	Cases: Under evaluation for cognitive impairment	Cases:	AD: NINCDS-ADRDA
	Non-comparative	%Male: 18%	47%			
	Prospective	Race: nd	nd			PD:
Country:	US	Other:		Controls:	Controls:	VascDz:
Setting:	Clinic					Other:
Funding:	nd					

* Diagnosed with Senile dementia of Alzheimer's type (SDAT)
** Non-SDAT

Predictor(s): (eg, B vit level)	Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
Plasma thiamine* ng/mL	MMSE	N enrolled:		nd	
RBC thiamine* ng/mL	Diagnosis of AD	N analyzed:		34	
		Drop-outs (%):			
Comments:					

*Microbiologic assay (*Kloeckera apiculata*). Thiamine deficient defined as below age-matched normal range.
Plasma: Normal mean (range): Age 61-80: 12.0 (8-26); Age 81+: 11.0 (10-12.6) ng/mL
RBC: Normal mean (range): Age 61-80: 146.0 (89-205); Age 81+: 140.0 (131-163) ng/mL

Other predictors/outcomes reported:			
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Authors note possibility that some "non-SDAT" patients may also have AD (in addition to other causes of dementia). Definition of low thiamine vague and age-dependent in a non-consistent manner (normal mean lower in elderly, but lower end of range higher).		
Quality (A/B/C):	C	Applicability (1/2/3):	2

Outcome(s):	Results (Text)
MMSE	There was no significant difference in MMSE scores between patients with probably SDAT with low plasma thiamine levels and those with normal plasma thiamine levels (*P*=0.11).

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Plasma B1 ng/mL		p	Plasma B1 Low*		p	RBC B1 ng/mL		p	RBC B1 Low*		p
		Mean	SD		n	%		Mean	SD		n	%	
SDAT	17	7.5	4.1	0.002	11	65%	<0.001	149.9	34.6	0.07	3	18%	0.70
Non-SDAT	17	12.6	5.4		2	12%		168.0	47.8		0	0%	

* Age 61-80: <8 ng/mL; Age 81+: <10 ng/mL
** Age 61-80: <89 ng/mL; Age 81+: <131 ng/mL

Correlation

Author, Year: Gold, 1998	**Ref ID**: 1120	**Vitamins**: Thiamine
Objective: To explore the extent of thiamine deficiency in neurodegenerative by determining the plasma and RBC thiamine levels in PD patients and comparing the results to a previous group of probable AD patients (Gold et al 1995)		

Study characteristics		Population p-AD		PD	Inclusion criteria	Exclusion criteria	Definitions	
Study design	XS	Age:	77.8+/-7.7	71.3 (8.7)	Cases:	Cases:	AD:	NINCDS/ADRDA criteria for probable AD
	Comparative	%Male:	18%	61%	AD recruited from Memory Disorders Clinic who were ambulatory and were living at home, either independently or with a dedicated caregiver. PD patients recruited from Movement Disorders Clinic. The inclusion criteria were age >50 and a diagnosis of Parkinson's disease. All patients were receiving dopaminergic meds and had significant clinical responses	Patients with any h/o gastric, digestive diseases, of gastric or intestinal resections, or of malabsorption syndrome	PD:	Clinically accepted criteria 2/3 cardinal features: tremor, bradykinesia, or rigidity
	Retrospective	Race:	nd	nd				
Country:	US	Other:			Controls: None	Controls:	VascDz:	
Setting:	Academic hospital						Other:	
Funding:	nd							
Comments:								

Predictor(s): (eg, B vit level)		Outcome(s): Definition:		Total	Population of interest AD	Population of interest PD	Control
Plasma thiamine*	ng/mL	Levels in AD patients	N enrolled:	50	17	33	
Erythrocyte thiamine*	ng/mL	Levels in AD patients	N analyzed:	50	17	33	
			Drop-outs (%):	nd			
Comments:							

* Non fasting levels assessed by using a bioassay (Lactobacilli agar)

Other predictors/outcomes reported:	None		
Follow-up duration (if applicable):	A group of PD patients compared to those with AD from a different year		
Reasons for drop out (if applicable):			
Limitations:			
Quality (A/B/C):	B	Applicability (1/2/3):	1

Outcome(s):	Results (Text)
Plasma thiamine levels	Statistical analysis demonstrated that patients with pAD had sig lower raw plasma thiamine levels ($p<0.001$) and lower z-score plasma thiamine levels ($p<0.01$) than patients with PD.
RBC thiamine levels	No significant differences were noted in the raw RBC thiamine levels or z score RBC thiamine levels between two groups of patients. A sig higher number of AD patients were plasma thiamine deficient than PD patients ($p<0.001$) No correlation between RBC and plasma thiamine levels for either group of patients

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Pl Thiamine ng/mL			*p*	RBC B1 ng/mL			*p*	MMSE scores 0-30				Pl B1 deficiency patients ng/mL			*p*
		Mean	SD	r=		Mean	SD	r=		Mean	SD	r=	P	Mean	SE/SD	Prevalence	
AD	17	7.5	4.1		<0.001	149.9	34.6		NS	17.6	7.7		<0.001			65%	
PD	33	11.06	4.08			146.8	43.1			26.8	4.1					9%	

Correlation

Author, Year: Goodwin, 1983	**Ref ID**: 1129	**Vitamins**: B1, riboflavin, B12, B6, folate
Objective: To examine the hypothesis that subclinical malnutrition may be associated with age-related changes in cognitive function		

Study characteristics		**Population**		**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age:	72 (60-94)	Ambulatory and living independently and recruited from Albuquerque area in early 1979 with 1) age of 60 yrs or older 2) no prescription medication or daily nonprescription meds 3) no known serious medical diagnoses eg cancer, aortic stenosis, diabetes or TIA while patients with osteoarthritis or cataracts included as long as they were not receiving medications	Those with serious medical diagnosis and on prescription meds (n=24); incomplete dietary intake, vitamin levels, or cognitive assessment (n=11); subjects died before administration of the cognitive tests (n=7)	AD:
	Non-comparative	%Male:	46%			PD:
	Prospective	Race:	ND			VascDz:
Country:	US	Other:	85% finished high school and 49% finished college			
Setting:	Academic hospital					Other:
Funding:	Gov and Private foundation					healthy
Comments:						

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		Total	Population of interest	Control
Folate, thiamine, riboflavin, pyridoxine, and vitamin B12 nutrient intake	Dietary intakes were measured by 3-day food record, weighting all food items on a portable scale.	Cognitive tests	Halstead-Reitan categories test	N enrolled:	304	304	
Folate, thiamine, riboflavin, pyridoxine, and vitamin B12 blood levels	Fasting blood samples. The assessment of thiamine and riboflavin was determined by a functional assay; ie, transketolase and glutathione reductase, respectively. Plasma levels of folate (RBC) and vitamin B12 were determined by competitive binding radioassays.		Wechsler verbal memory test	N analyzed:	260	260	
				Drop-outs (%):	14%		
Dietary intake categories	Bottom 5%, bottom 10%; top 90%						
Comments:	Halstead Reitan categories test was a nonverbal automated test of abstract thinking and problem solving ability and sensitive indicator for minimal changes in mental status All correlations were controlling for age and sex of the subjects.						

Other predictors/outcomes reported:	Protein intake, vitamin C intake and blood levels		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Data analyze for completers only. No means of intakes or blood levels were reported.		
Quality (A/B/C):	B	Applicability (1/2/3):	2

Outcome(s):	Results (Text)
Mean scores of halstead Reitan Categories test	There was a trend for those subjects in the bottom 5% or 10% of dietary intake of all nutrients to do poorly on the test compared with the rest of the population except for folate
Mean scores of Wechsler Memory test	There was a trend for those subjects in the bottom 5% or 10% of dietary intake of all nutrients to do poorly on the test compared with the 90% of the population
Mean scores of halstead Reitan Categories test	There was a trend for those subjects in the bottom 5% or 10% of blood levels of specific nutrients riboflavin, vit B12 and folic acid to do poorly on the test compared with the rest of the population

Mean scores of Wechsler Memory test	Statistically significant deficiencies in performance were seen in those with low levels of vit B12

Correlation of dietary intake levels of B vitamins with cognitive function (cross-sectional studies)

Description of (Sub-) Groups	N	Folate r=	*p*	Thiamine r=	*p*	Riboflavin r=	*p*	Pyridoxine r=	*p*	Vit B12 r=	*p*
Halstead Reitan Categories test	260	.00	NS	-.02	NS	.05	NS	-.04	NS	-.04	NS
Wechsler verbal memory test	260	-.06	NS	-.02	NS	.02	NS	-.02	NS	-.02	NS

Correlation of blood levels of B vitamins with cognitive function (cross-sectional studies)

Description of (Sub-) Groups	N	Sr Folate Mean	SE/SD	ND r=	*p*	Sr Thiamine Mean	SE/SD	ND r=	*p*	Sr Riboflavin Mean	SE/SD	ND r=		Sr B 12 Mean	SE/SD	ND r=	*p*
Halstead Reitan Categories test	260			0.08	NS			.02	NS			.02	NS			.02	NS
Wechsler verbal memory test	260			-.03	NS			-.04	NS			.14	<0.05*			.00	NS

* Remained sig in a multivariate analysis controlling for age and sex of the subjects

Correlation

Author, Year: Gottfries, 2001	**Ref ID**: 1145	**Vitamins**: B12, Folate
Objective: Correlation of B vitamins (etc.) with cognitive impairment		

Study characteristics		**Population**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age: 70.4	Cases: Ambulatory, age ≥50 yr, complaining about cognitive disturbances in an outpatient memory clinic.	Cases: Plasma B12 >600 pmol/L, Plasma folate > 30 nmol/L, or Serum creatinine >100 nmol/L (to exclude those taking supplements or with insufficient kidney excretion, thus elevating homocysteine)	Alzheimer Type of Dementia (DAT):	DSM-IV, NINCDS-ADRDA
	Comparative	%Male: 46%				
	Prospective	Race: nd			Mild Cognitive Impairment:	Cognitive impairment not severe enough to meet criteria for dementia
Country:	Sweden	Other:	Controls:	Controls:	Vascular Dementia (VAD):	NINDS-AIREN
Setting:	Outpatient memory unit				Subjective Memory Complaints:	Complaints were not confirmed by psychological testing
Funding:	nd					
Comments:						

VAD = vascular dementia

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Plasma B12*	pmol/L	4 diagnostic groups	As defined above	N enrolled:			
CSF B12**	pmol/L			N analyzed:			
CSF B12/Blood B12***	x1000						
Plasma Folate****	nmol/L						
Blood Folate*****	nmol/L			Drop-outs (%):			
Comments:							

* No data on measurement method. Normal range 150-700 pmol/L
** No data on measurement method. Normal range is unknown.
*** Normal range is unknown
**** No data on measurement method. Normal range 6-39 nmol/L
***** No data on measurement method. Normal range 140-380 nmol/L

Other predictors/outcomes reported:	Serum and CSF Homocysteine, Serum and CSF MMA, CSF Tau protein, CSF/Serum albumin ratio, Brain imaging pathology, vascular risk factors, EEG		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Reported values are not adjusted for potential confounders. Numbers of subjects in each analysis unclear		
Quality (A/B/C):	C	Applicability (1/2/3):	3

Outcome(s):	Results (Text)

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N*	Plasma B12 pmol/L Mean	SD	*p*	Plasma B12 % <150 pmol/L	*p*	CSF B12 pmol/L Mean	SD	*p*	CSF/Plasma B12 Mean	SD	*p*
DAT	≤43	355.8	130.9		0%		13.9	10.0		39.8	22.5	
Mild Cog Impair	≤32	295.8	93.6	NS	6.3%	NS	11.3	5.8	NS	40.1	19.9	NS
VAD	≤14	272.2	105.5		7.7%		10.8	6.3		39.9	18.8	
Subj Memory Compl	≤12	330.2	113.3		8.3%		14.4	6.4		49.8**	28.2	

* 101 in total cohort (43+32+14+12). However, Plasma B12 had N=99; CSF B12 had N=80.
** "Numerically higher [than other groups], which would suggest a better transport of vitamin B12 into the brain in this group."

Description of (Sub-) Groups	N*	Plasma Folate nmol/L Mean	SD	*p*	Plasma Folate % <6 nmol/L	*p*	Blood Folate nmol/L Mean	SD	*p*	Blood Folate % <140 nmol/L	*p*
DAT	≤43	12.2	4.5		0%		237.5	78.7		5.9%	
Mild Cog Impair	≤32	14.1	6.9	NS	6.3%	NS	253.8	90.0	NS	4.2%	NS
VAD	≤14	11.4	4.6		7.7%		267.0	145.5		0%	
Subj Memory Compl	≤12	12.7	5.1		0%		282.5	86.5		0%	

* 101 in total cohort (43+32+14+12). However, Plasma Folate had N=98 and Blood Folate had N=74.

Correlation

Author, Year: Haller, 1996	**Ref ID**: 1239	**Vitamins**: Folate and Cobalamin
Objective: Assessment of the mental health of the European elderly and its correlations with micronutrient plasma levels, education and ability to carry out activities of daily living		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age:		Cases:	Cases:	AD:
	Non-comparative	%Male: 49%		Randomized sample of both sexes born in the period 1913 to 1918.		PD:
	Prospective	Race:				
Country:	9 European countries	Other:		Controls:	Controls:	VascDz:
Setting:						Other:
Funding:						
Comments:						

Predictor(s): (eg, B vit level)	Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
folate	MMSE score	N enrolled:	885	885	
cobalamin	MMSE score	N analyzed:	885	885	
		Drop-outs (%):			
Comments:					

Other predictors/outcomes reported:	
Follow-up duration (if applicable):	
Reasons for drop out (if applicable):	
Limitations: method of randomization not stated	
Quality (A/B/C): C	Applicability (1/2/3): 3

Outcome(s):	Results (Text)
	There were highly significant but weak correlations between the total MMSE scores and the coblamin and folate plasma levels.

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	(Sr/CSF) folate (unit)		*p*	(Sr/CSF) cobalamin (unit)		*p*
		Mean	SE/SD	r=	Mean	SE/SD	r=
MMSE overall	885			0.103 <0.01			0.125 <0.001
MMSE men	433			ND			0.161 <0.001
MMSE women	452			0.113 <0.05			ND

Correlation

Author, Year: Jelicic, 2002	**Ref ID**: 1498	**Vitamins**: Vitamin B12 and folate
Objective: To examine the effects of low levels of vitamin B12 and folate in older adults on speed of information processing and memory		

Study characteristics		Population	Controls	Inclusion criteria	Exclusion criteria	Definitions
Study design	XS	Age: 68.7		Cases:	Cases:	AD:
	Comparative	%Male: 47%		Non-demented older people who underwent blood tests		
	Retrospective	Race:				PD:
Country:	The Netherlands	Other:		Controls:	Controls:	VascDz:
Setting:	Genral population					Other:
Funding:	Dutch Ministry of Health, Welfare and Sports					
Comments:						

Predictor(s): (eg, B vit level)	Outcome(s):	Definition:		Total	Population of interest	Control
Group 1: normal B12 & folate levels	Memory and speed of information processing		N enrolled:	698		
Group 2: normal B12 & low folate levels			N analyzed:	698		
Group 3: low B12 & normal folate			Drop-outs (%):	0		
Group 4: low B12 & folate						
Comments: There were differences between the study groups with respect to age and education.						

Other predictors/outcomes reported:			
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:			
Quality (A/B/C):	B	Applicability (1/2/3):	2

Outcome(s):	Results (Text): ANOVA was used to determine whether the 4 groups differed with regard to cognitive performance using age and education as covariates.
	1. No significant differences in memory performance were found.
	2. Borderline significant differences (p=0.087) between the 4 groups with respect to speed of information processing were found.
	3. Post hoc analyses using ANOVA with age and education as covariates showed that Group 1 (normal B12 & folate) exhibited better performance on the coding task than group 3 (low B12 only), p<0.05.
	4. The other post hoc analyses were not significant.
	5. ANOVA with age and education as covariates revealed that particpants with normal B12 outperformed those with low B12 on coding task.

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	**N**	**Memory score**		**(unit)**	***p***	**Speed of information processing**		**(unit)**	***p***
		Mean	**SD**	**r=**		**Mean**	**SD**	**r=**	
Group 1: normal B12 & folate	469	19.9	6.1			38.8	11.7		
Group 2: normal B12, low folate	100	18.7	5.5			36.1	9.7		
Group 3: low B12, normal folate	98	18.6	5.6			34.1	11.1		
Group 4: low B12 & folate	31	16.9	4.2			30.3	10.8		

Correlation

Author, Year: Jimenez-Jimenez, 1999	**Ref ID**: 1507	**Vitamins**: thiamine
Objective: To assess the lumbar CSF levels of thiamine and their phosphate esters in pts with PD compared with a control population		

Study characteristics		Population		Controls	Inclusion criteria	Exclusion criteria	Definitions
Study design	XS	Age:	64	63	Cases: PD	Cases: Vitamin in last 6 mo, ETOH >80 g/day in last 6 mo, previous hx of chronic liver disease, CRF, gastrectomy, pancreatic diseases, malabsorption, atypical diets, undernutrition, severe systemic disease	AD:
	Comparative	%Male:	58	40			PD: Diagnosed; details not provided
	Retrospective	Race:	ND	ND			
Country:	Spain	Other:			Controls: 'healthy': suspected subarachnoid hemorrhage, psuedotumor cerebri, oculomotor palsies or other neurological dx that required LPs	Controls: Same as above	VascDz:
Setting:	2 urban hospitals						Other:
Funding:	Comunidad de Madrid & Fundacion Neurociencias y Envejecimiento						
Comments:	7/24 pts with PD untreated; control population had suspected neurological problems other than PD						

Predictor(s): (eg, B vit level)	Outcome(s): Definition:		Total	Population of interest	Control
Free and total thiamine		N enrolled:	64	24	40
Thiamine-diphosphate		N analyzed:	64	24	40
Thiamine-monophosphate		Drop-outs (%):	0		
Comments:					

Analysis of thiamine by ion-pair reversed phase HPLC according to Bettendorff et al.

Other predictors/outcomes reported:	
Follow-up duration (if applicable):	
Reasons for drop out (if applicable):	
Limitations: control group not healthy	
Quality (A/B/C): C	Applicability (1/2/3): 3

Outcome(s):	Results (Text)
	1. The mean CSF levels of thiamine-diphosphate, thiamine-monophosphate, and total thiamine of PD pts did not differ significantly from those of controls, although free CSF thiamine levels were significantly lower in the PD patient group. 2. PD pts treated with levodopa had significantly higher CSF thiamine-diphosphate and total thiamine than those not treated with this drug. 3. No significant correlation in PD pts between the CSF thiamine (in all their forms) and age, age at onset of PD, duration of PD, scores of the Activities of Daily Living and motor examination, and the Hoehn and Yahr staging. 4. There was no correlation between CSF thiamine levels and the analyzed clinical features of PD.

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	CSF Thiamine-diphosphate (nmol/L)		*p*	CSF Thiamine-monophosphate (nmol/L)		*p*	CSF Free thiamine (nmol/L)		*p*	CSF Total thiamine (nmol/L)		*p*
		Mean	SD		Mean	SD		Mean	SD		Mean	SD	
PD	24	3.9	3.0		4.3	3.3		0.9	1.3		9.1	6.4	
Control	40	3.1	2.3		4.3	2.9		1.9	1.4	<0.01	9.3	5.1	
PD (+)L-DOPA	15	5.1	3.1		5.2	3.6	<0.01	1.1	1.6		11.5	6.7	<0.01
PD (-)L-DOPA	9	2.0	1.5		2.8	2.1		0.4	0.3		5.2	3.7	

Correlation

Author, Year: Jones, 2002	**Ref ID**: 1533	**Vitamins**: B12, folic acid
Objective: To examine the variability in rate of decline during the last 3 yr before the diagnosis of AD could be linked to participant characteristics within demographic, health related, genetic and social domains		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Longitudinal	Age: ND		Cases: All inhabitants aged ≥75 yrs and older in the Kungsholmen Parish of Stockholm, Sweden	Cases:	AD: ND
	Non-comparative	%Male: ND				
	Prospective	Race: Probably white				PD:
Country:	Sweden	Other:		Controls:	Controls:	VascDz:
Setting:	Community based					Other:
Funding:	ND					
Comments:						

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Vit B12	ND	MMSE (Swedish version)	0-30	N enrolled:	230	230	
Folate	ND			N analyzed:	230	230	
				Drop-outs (%):			
Comments:	MMSE (Swedish version) administered both at baseline and at follow-up						

Other predictors/outcomes reported:	Demographic factors; disease measures; depression; ApoE genotype		
Follow-up duration (if applicable):	3 yr		
Reasons for drop out (if applicable):			
Limitations:	Very incomplete description of results		
Quality (A/B/C):	C	Applicability (1/2/3):	3

Outcome(s):	Results (Text)
Cognitive decline	Vitamin status (B12 and folate) did not precipitate (ie, not associated with) the decline

Correlation

Author, Year: Joosten, 1997	**Ref ID**: 1536	**Vitamins**: B12, Folate
Objective: B12, Folate, MMA in AD and controls		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS/Longitudinal	Age: 82.8+/-4.9	1. 81.1+/-5.8 2. 79*+/-5.9	Cases: Age >70 y, admitted to acute geriatric ward, screened in for probable AD	Cases: Vitamin supplement, blood transfusion, life-threatening disease	AD: DSM-III-R and NINCDS-ADRDA MMSE<21 Hachinski<4
	Comparative	%Male: 37%	1. 42% 2. 33%			
	Prospective	Race: nd	nd			
Country:	Belgium	Other:		Controls: 1. Age >70 y, admitted to acute geriatric ward, screened out for probable AD, age and sex matched 2. Age >70 y, healthy, living at home independently	Controls: 1. Vitamin supplement, blood transfusion, life-threatening disease 2. Same as 1 + Malignancy, vascular disorder	
Setting:	Hospital and Home					
Funding:	Pharmaceutical					
Comments:						

* Significantly different than AD (P<0.001)

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Serum Vit B12*	ng/L	AD diagnosis		N enrolled:	151	52	1. 50 2. 49
Serum Folate**	µg/L			N analyzed:	151	52	1. 50 2. 49
MMA	nmol/L			Drop-outs (%):			
Hcy	µmol/L						
Comments:							

* Amersham, radioimmunoassay. Normal range 140-550 ng/L.
** Amersham, radioimmunoassay. Normal range 2.4-7.2 µg/L.

Other predictors/outcomes reported:			
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:			
Quality (A/B/C):	C	Applicability (1/2/3):	2

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Serum B12 ng/L		p	Serum B12 <139 ng/L	p	Serum Folate µg/L		p	Serum Folate <2.4 µg/L	p
		GeoMean	95% range	r=	Prevalence		GeoMean	95% range	r=	Prevalence	
AD	52	284	(80-999)	NS	3.8%	NS	3.5	(1.3-9.7)	NS	21.2%	0.042
Hospitalized, non-AD	50	281	(89-887)		10%		4.0	(1.5-10.9)		14%	NS
Healthy	49	284	(119-673)		6.1%		3.8	(1.8-8.2)		6.1%	NS

GeoMean, geometric mean

Correlation

Author, Year: Malaguarnera, 2004	**Ref ID**: 1972	**Vitamins**: Pyridoxal phosphate levels
Objective: To evaluate the relationship between the plasma Hcy levels and the vitamins involved in its metabolism in cognitive disorders		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	72.6 (7.38)	73.7 (4.2)	Cases:	Cases:	AD:	NINCDS-ADRDA criteria and also confirmed by cerebral CT or MRI that showed cortical atrophy and normal aspects of the white matter in all patients
	Comparative	%Male:	32%	50%	AD patients: all those who presented with progressive cognitive deficit for at least one year VascDz: ND		PD:	
	Prospective	Race:	ND	ND				
Country:	Italy	Other:			Controls:	Controls:	VascDz:	NINDS-AIREN criteria and confirmed radiologically by subcortical lacunaes and/or multiple involvement of the inner white matter
Setting:	Academic hospital				ND		Other:	
Funding:	ND						Normal healthy	Clinically and MMSE score to rule out cognitive impairment
Comments:	(B12 and folate not extracted as total n<100)							

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest***	**Control**
Pyridoxal phosphate levels	nmol/L	Dementia	AD	N enrolled:	68	22	24
				N analyzed:	68	22	24
				Drop-outs (%):			
Comments:	* included only patients with AD and healthy (vascdz n=22 not included)						

PLP measured by radio-enzymatic assay

Other predictors/outcomes reported:	Hcy, folate, vit B12, cholesterol, HDL, TG, LDL		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Small N and XS		
Quality (A/B/C):	C	Applicability (1/2/3):	1

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	**N**	**Sr**	**PLP**	**nmol/L**	***p***			
		Mean	**SD**					
AD	22	52.0	10.78		NS			
Healthy controls	24	57.5	8.19					

Correlation

Author, Year: Mastrogiacoma, 1996	**Ref ID**: 2032	**Vitamins**: B1
Objective: To evaluate the status of brain thiamine and its phosphate esters in AD		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	73 (2)	70 (3)	Cases:	Cases:	AD:	Presence of both neuritic plaques and neurofibrillary tangles in both neocortex and hippocampus in the absence of any degenerative process
	Comparative	%Male:	ND	ND	Tissues from the autopsied brains of confirmed patients with AD	ND		
	Retrospective	Race:	ND	ND			PD:	
Country:	Canada and Belgium	Other:			Controls:	Controls:	VascDz:	
Setting:	Academic hospital				neurologically and histopathologically normal control subjects matched with respect to age, post mortem status, premortem agonal status, cerebral cortical pH and lactic acid levels	ND	Other:	
Funding:	Multi Gov funds and student award							
Comments:								

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Free non-phosphorylated thiamine	ND	Cerebral cortical levels (temporal, parietal, occipital)		N enrolled:	38	20	18
Total thiamine	ND			N analyzed:	38	20	18
				Drop-outs (%):			
Comments:							

Other predictors/outcomes reported:	Thiamine dependent enzymes		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Autopsy study and no correlation with sr levels		
Quality (A/B/C):	C	Applicability (1/2/3):	1

Outcome(s):	Results (Text)
Total thiamine	Levels of total thiamine were normal in all three brain areas, a non significant trend towards reduction predominantly in the temporal and occipital cortices

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Temporal cortex Thiamine pmol/mg of protein			*p*	Temporal cortex Total thiamine pmol/mg of protein			*p*		
		Mean	SE	% of change		Mean	SE	% of change			
AD	20	9.0	0.7	-1	NS	27.2	1.4	-11	NS		
Controls	18	9.0	0.7		NS	30.7	1.3		NS		

Description of (Sub-) Groups	N	Parietal cortex Thiamine pmol/mg of protein			*p*	Parietal cortex Total thiamine pmol/mg of protein			*p*		
		Mean	SE	% of change		Mean	SE	% of change			
AD	20	9.9	0.8	+9	NS	29.5	1.4	-5	NS		
Controls	18	9.1	0.6		NS	31.1	1.3		NS		

Description of (Sub-) Groups	N	Occipital cortex Thiamine pmol/mg of protein			*p*	Occipital cortex Total thiamine pmol/mg of protein			*p*		
		Mean	SE	% of change		Mean	SE	% of change			
AD	20	10.1	0.8	-8	NS	27.9	1.4	-12	NS		
Controls	18	11.0	0.7		NS	31.6	1.3		NS		

Total thiamine=thiamine monophosphate+thiamine+thiamine diphophate

Correlation

Author, Year: Maxwell, 2002	**Ref ID**: 2072	**Vitamins**: Folate
Objective: Association of folate level with future dementia		

Study characteristics		**Population**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	Longitudinal	Age: 80.1 SD 7.3	Cases: Canadian Study of Health and Aging (CSHA). Representative sample of Canadians aged 65 years and older. 18 centers in 5 regions across Canada. Both community and residents of institutions. All subjects scoring <78 on Modified Mini-Mental State (3MS) examination, random sample of those scoring ≥78, subjects unable to be screened, all institutionalized subjects invited for comprehensive clinical examination. No clinical dementia (at baseline) per DSM-III-R. Available folate data Re-contacted after 5 years.	Cases:	AD:	nd (?DSM-III-R)
	Non-comparative	%Male: 45%				
	Prospective	Race: nd			PD:	
Country:	Canada	Other:			VascDz:	
Setting:	Community and Institutions				Cognitively impaired but not dementia; Dementia:	DSM-III-R
Funding:	Government; Pharmaceutical					
Comments:						

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**
Folate quartile (by study center)*	Q1: <5-12 nmol/L	Modified Mini-Mental State (3MS), Baseline	0-100	N met inclusion criteria:	523
	Q4: >14-36 nmol/L	Cognitive decline	Δ 3MS ≥10	N analyzed:	226-266
		Dementia	DSM-III-R	Not analyzed (%):	~50%
		AD	?DSM-III-R		
Comments:					

* ND on measurement method or normal range.

Other predictors/outcomes reported:	Adverse cerebrovascular event (primary outcome), death, institutionalized		
Follow-up duration (if applicable):	5 years		
Reasons for drop out (if applicable):	Newfoundland (legal restrictions) 33; missing clinical data 47; no data 177-217		
Limitations:	High proportion of unanalyzed subjects, without explanation		
Quality (A/B/C):	B	Applicability (1/2/3):	2

Correlation of Predictors with Outcomes

Outcome	N	All		N	Q1 Folate <5-12 nmol/L		N	Q2 Folate (nd)		N	Q3 Folate (nd)		N	Q4 Folate >14-36 nmol/L		Q1 v Q4
		Mean	SD		Mean	SD		Mean	SD		Mean	SD		Mean	SD	
Baseline 3MS Score	369	74.8	15.8	80	66.6	19.2							100	77.8	11.4	$P \leq 0.0001$
3MS Decline (5 yr)	266	N=87		nd	43.5%		nd	32.4%		nd	29.3%		nd	29.7%		OR 2.16 (0.96, 4.86)
Dementia (incident)	243	N=66		nd	38.1%		nd	27.3%		nd	23.1%		nd	24.3%		OR 2.19 (0.93, 5.15)
AD (incident)	226	N=49		nd	33.3%		nd	21.3%		nd	15.3%		nd	20.9%		OR 2.17 (0.85, 5.53)

* Odds Ratio (95% confidence interval), adjusted for age and sex.

Correlation

Author, Year:	McCaddon, 2004	**Ref ID**:	2088	**Vitamins**:	B12
Objective:	Association of B12 and transcobalamin polymorphism with AD (Clinical study)				

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age:	79 (75-84)	79 (73-84)	Cases:	Cases:	AD: DSM-IV
	Comparative	%Male:	30%	38%	Features compatible with DSM-IV criteria for primary degenerative dementia of Alzheimer type	Receiving B12 supplementation (for B12 correlation)	
	Prospective	Race:	nd				PD:
Country:	UK	Other:			Controls: Healthy, cognitively intact, age and sex matched elderly volunteers from a General Practice in a comparable SES area.	Controls:	VascDz:
Setting:	Dementia clinic, outpatient						Other:
Funding:	Government						
Comments:							

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**AD**	**Control**
B12, serum*	ng/L	AD diagnosis		N enrolled:	144	70	74
Holo-transcobalamin**	pmol/L			N analyzed:	136	65	71
Transcobalmin isotype	TC 776C>G			Drop-outs (%):	6%	7%	4%
Comments:							

* Bayer ACS:180 SE, chemiluminescence. ND on normal mean or range.
** Axis-Shield, solid-phase capture assay. ND on normal mean or range.

Other predictors/outcomes reported:	Holo-TC levels (the ability of transcobalamin to bind to cobalamin)		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):	nd		
Limitations:	Numbers of subjects analyzed for B12 unclear. Unclear why dropouts. Combination of clinical and histopathology (with large # unanalyzed of autopsy cases) problematic		
Quality (A/B/C):	C	Applicability (1/2/3):	3

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Sr B12 ng/L Mean	range	*p*	Sr Holo-TC ng/L Mean	range	*p*	N	776CC %	776CG %	776GG %	*p*	776C Allele Frequency	776G Allele Frequency	*p*
AD	47*	333	272-420		43	(30-62)		65	25%	52%	23%		0.51	0.49	
Healthy control	74	342	296-455		52	(33-77)		71	37%	51%	12%		0.62	0.38	
difference:				0.23			0.18					NS**			0.15**

* 23 subjects receiving B12 supplementation were excluded. Unclear if all had AD, but we assume this to be the case.
** The distribution is in Hardy-Weinberg equilibrium. There is a non-significant increase in TC776G allele frequency in the clinically diagnosed AD group.

Survival Curve Evaluation of Combined Clinical and Histopathology Studies

Outcome(s):	Results (Text)
Age of disease onset	N (AD)=74 clinical (living) + 35 histopathology cases (autopsy) N (Control)=70 clinical + 107 histopathology AD-free survival significantly greater for 776CC than either 776GG (*P*=0.008) or 776CG (*P*=0.02). Proportionately fewer people with 776CC appeared to develop AD at any given age.

Correlation

Author, Year: McCaddon, 2004	**Ref ID**: 2088	**Vitamins**: B12
Objective: Association of B12 and transcobalamin polymorphism with AD (Histopathology study)		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Median Age (at death):	80 (75-85)	78 (70-83)	Cases:	Cases:	AD:	CERAD criteria
	Comparative	%Male:	38%	53%	Histopathologically confirmed AD post-mortem (CERAD criteria)			
	Retrospective	Race:	nd	nd			PD:	
Country:	Sweden	Other:			Controls:	Controls:	VascDz:	
Setting:	Autopsy (Brain bank)				Died from cardiac disease or malignancy. No history of dementia or neuropsychiatric diseases	Macroscopic infarcts, AD	Other:	
Funding:	Government							
Comments:								

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**AD**	**Control**
Transcobalmin isotype	TC 776C>G	AD diagnosis		N enrolled:	201	94	107
				N analyzed:	201	94	107
				Drop-outs (%):			
Comments:							

Other predictors/outcomes reported:	ApoE genotype		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Autopsy study with matched controls from brain bank; unadjusted		
Quality (A/B/C):	C	Applicability (1/2/3):	1

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	776CC	776CG	776GG	*p*	776C	776G	*p*
		%	%	%		Allele Frequency		
AD	94	34%	48%	18%		0.58	0.42	
Non-AD control	107	39%	47%	14%		0.63	0.37	
difference:					NS			NS

See McCaddon 2004 RefID 2088 for combined study survival curve.

Correlation

Author, Year: Miller, 2002	**Ref ID**: 2167	**Vitamins**: B12, folate, B6
Objective: To investigate plasma Hcy, B6 status and the occurrence of vascular disease in patients with AD		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	Case-control	Age:	79 ±7	75 ± 6	Cases:	Cases:	AD:	According to NINCDS/ARDRA criteria (REF 11)
	Comparative	%Male:	35	46	Subjects with Dx of possible or probable AD	ND		
	Retrospective	Race:	ND	ND			PD:	
Country:	US	Other:			Controls:	Controls:	VascDz:	
Setting:					Volunteers of similar age without Dx of AD or other major neurodegenerative disease	ND	Other:	
Funding:	Government						Coexisting vascular disease (VD):	Hx stroke, MI, angina, CHF, CAD, TIA or presence of cerebral infarction documented on CT or MRI
Comments:								

Predictor(s): (eg, B vit level)	Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Plasma PLP	AD	NINCDS/ARDRA criteria	N enrolled:	80	43	37
			N analyzed:	80	43	37
			Drop-outs (%):	ND	ND	ND
Comments:	Serum PLP was determined by radioenzymatic assay (ALPCO, Windham, NH); considered as low when value <25nmol/L					

Other predictors/outcomes reported:	Age, gender, RBC folate, plasma B12, serum CRE, serum TSH, medication use (Aricept or B vit supplements)		
Follow-up duration (if applicable):	N/A		
Reasons for drop out (if applicable):			
Limitations:	Statistically significant difference for age between cases and controls; unclear whether controls recruited from the same community as cases; power calculation not reported		
Quality (A/B/C):	B	Applicability (1/2/3):	2

Outcome(s):	Results (Text)
Low PLP (<25nmol/L)	The OR for low plasma PLP was 12.3 for patients with AD compared with subjects without AD. VD was not significantly associated with low PLP, nor did VD significantly modify the odds among those subjects with AD.

Correlation of Predictors with Outcomes (case control studies)

Odds ratios for low PLP (<25nmol/L) in patients with AD and control subjects

Description of (Sub-) Groups	N	OR (Adj 1*)		
AD	43	12.3	1.8-84	p=0.01
AD with VD (vs. AD without VD, n=32)	11	3	0.46-19	p=0.25
VD (AD, n=11 and normal, n=15)	26	0.55	0.12-2.5	p=0.43

* Adj 1, adjusted for age, gender, RBC folate, plasma B12, serum CRE, serum TSH, plasma Hcy

Correlation

Author, Year: Miller, 2003	**Ref ID**: 2170	**Vitamins**: Homocysteine, B-vitamin
Objective: To investigate the effect of L-DOPA and B-vitamin status on plasma homocysteine in PD pts		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age: 64	60	Cases:	Cases:	AD:
	Comparative	%Male: 65%	50%	> 30 yr,	Pregnancy; OCP; other neurodegenerative diseases; malnutrition, depression or psychotic illnesses, other major medical disorders	PD: Two out of three: rigidity, resting tremor and bradykinesia
	Prospective	Race:				
Country:	US	Other:		Controls:	Controls:	VascDz:
Setting:	University outpatient clinic					Other:
Funding:	US government grants					
Comments:	Self-reported use of folate, B-12 or B-6 was similar between groups; more pts in treatment group on MAO B inhibitor or a dopamine receptor agonist than in the control group					

Predictor(s): (eg, B vit level)	Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
L-DOPA treated PD pts	homocysteine	N enrolled:	40	20	20
Controls: PD pts not treated with L-DOPA	folate	N analyzed:	40		
	B-12	Drop-outs (%):			
	Pyridoxal-5'-phosphate (PLP)				
Comments:					

Other predictors/outcomes reported:	
Follow-up duration (if applicable):	
Reasons for drop out (if applicable):	
Limitations:	
Quality (A/B/C): B	Applicability (1/2/3): 2

Outcome(s):	Results (Text)
	Plasma homocysteine was higher in treatment group than control (p=0.018).
	Plasma PLP was lower in treatment group than control (p=0.008).
	L-DOPA treated group: homocysteine vs. folate, R^2=0.487, p<0.001; homocysteine vs. vitamin B12, R^2=0.498, p<0.001; homocysteine vs. PLP, R^2=0.342, p=0.007. No correlation in the control group.

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	**N**		**plasma folate nmol/L *p***			**plasma B-12 pmol/L**			**plasma PLP nmol/L *p***			
			Mean	**SD**	**r=**	**Mean**	**SD**	**r=**	**Mean**	**SD**	**r=**	
L-DOPA treated	20		12.8	11.6		375	167		78	99.1		0.008
No L-DOPA	20		12.6	10.8		464	249		154	150		

Correlation

Author, Year: Mizrahi, 2004	**Ref ID**: 2189	**Vitamins**: B12, Folate
Objective: B12, Folate, Hcy in AD and healthy		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Year of birth:	1915*+/- 7.0	1927*+/- 7.0	Cases:	Cases:	AD: DSM-IV
	Comparative	%Male:	39%	48%	AD, Arab villagers,		
	Prospective	Race:	Arab	Arab			PD:
Country:	Israel	Other:			Controls:	Controls:	VascDz:
Setting:	Rural				Healthy, Arab villagers,	Memory complaints, indications of any inflammatory disorder	Other:
Funding:							
Comments:	This region has a high prevalence of AD despite low ApoE ε4 allele frequency						

*P<0.001 between groups

Predictor(s): (eg, B vit level)		Outcome(s): :		**Total**	**Population of interest**	**Control**
Plasma B12*	pmol/L	AD Dx	N enrolled:	235	79	156
Plasma Folate**	nmol/L		N analyzed:	230	75	155
(Plasma Hcy	μmol/L)		Drop-outs (%):	2%	5%	1%
Comments:						

* ICN Pharmaceuticals, radioisotope dilution assay. B12 deficiency defined as <125 pmol/L.
** ICN Pharmaceuticals, radioisotope dilution assay. Folate deficiency defined as <3.6 nmol/L.

Other predictors/outcomes reported:			
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):	2 Outlier Hcy (>54 μmol/L), 2 Outlier B12 (>850 pmol/L), 1 Hcy not available		
Limitations:			
Quality (A/B/C):	A	Applicability (1/2/3):	3

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Plasma Folate nmol/L Mean	SD	r=	*p*	Plasma B12 pmol/L Mean	SD	r=	*p*		
AD	75	4.3	(3.2)		NS	322.9	(136.0)		NS		
Healthy	155	4.8	(2.6)			350.5	(175.3)				

Description of (Sub-) Groups	N	(Outcome) OR (Adj 1*)					
Plasma B12 >259.95 pmol/L	230	1					
Plasma B12 203.70-259.95 pmol/L		0.7	(0.3-1.9)				
Plasma B12 <203.70 pmol/L		1.3	(0.5-3.4)				
Plasma Folate >11.40 nmol/L	230	1					
Plasma Folate 7.87-11.40 nmol/L		1.3	(0.5-3.7)				
Plasma Folate <7.87 nmol/L		1.6	(0.6-4.2)				

* Adj 1, adjusted for year of birth and gender

Correlation

Author, Year: Molina, 2002	**Ref ID**: 2196	**Vitamins**: B1
Objective: To assess the lumbar CSF levels of thiamine and their phosphate esters in patients with sporadic AD compared with a control population and to relate the decreased levels with increased risk of AD		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS and Longitudinal	Age: 72.6 (8.8)	70.2 (7.6)	Cases:	Cases:	AD: By DSM-IV; probable AD according to NINCDS-ADRDA; MMSE<23; Hachinski ischemic score <4 points; Hamilton's depression scale <17 points
	Comparative	%Male: 46%	44%	Unselected patients recruited during their first visit to neurology clinic in 2 hospitals in Madrid and fulfilling diagnostic criteria of AD	Therapy with vit supplements in the past 6 mo; ethanol intake >80g/d in past 6 mo; previous h/o chronic illnesses; atypical dietary habits; undernutrition; and previous h/o severe systemic disease	
	Prospective and retrospective analysis for progression	Race: ND	ND			PD:
Country:	Spain	Other: 24.4 BMI (4.7)	28.2 (3.4)	Controls:	Controls:	VascDz:
Setting:	Academic hospital			Healthy non-demented and those with normal CSF finding	Same as above	Other:
Funding:	Private non industry					
Comments:						

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Plasma thiamine	Nmol/L	MMSE	<23 for AD	N enrolled:	65	33	32
CSF thiamine	Nmol/L			N analyzed:	65	33	32
				Drop-outs (%):	0		
Comments:	Plasma and CSF thiamine was analyzed by ion pair reversed phase high performance liquid chromatography; normal reference level ND						

Other predictors/outcomes reported:			
Follow-up duration (if applicable):	Unclear; per yr progression for AD available		
Reasons for drop out (if applicable):	NA		
Limitations:	Unclear how per yr progression was assessed for 20 patients		
Quality (A/B/C):	C	Applicability (1/2/3):	3

Outcome(s):	Results (Text)
MMSE	Significant correlation between MMSE and plasma thiamine diphosphate r=0.41, p<0.05 Free thiamine correlated significantly with MMSE in both AD patients r=0.84; p<0.01 and controls r=0.40, p<0.05

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	CSF TDP nmol/L			*p*	CSF TMP nmol/L			*p*	CSF Free thiamine nmol/L			*p*	CSF Total thiamine nmol/L			*p*
		Mean	SD	r=		Mean	SD	r=		Mean	SD	r=		Mean	SD	r=	
AD	33	2.55	1.70		NS	3.57	3.84		NS	1.17	3.03		NS	7.29	6.98		NS
Controls	32	3.21	2.28			4.30	2.40			2.20	3.20			9.46	4.52		

Description of (Sub-) Groups	N	Sr TDP nmol/L			*p*	Sr TMP nmol/L			*p*	Sr Free thiamine nmol/L			*p*	Sr Total thiamine nmol/L			*p*
		Mean	SD	r=		Mean	SD	r=		Mean	SD	r=		Mean	SD	r=	
AD	33	2.22	1.74		<.05	1.32	2.02		NS	1.16	1.21		<.05	4.75	7.72		<.05
Controls	32	3.23	1.87			2.20	3.20			2.61	2.93			7.88	5.79		

Correlation

Author, Year: Morris, 2001	**Ref ID**: 2229	**Vitamins**: folate
Objective: To evaluate the relation between serum tHcy and performance on short delayed-recall tests of elderly men and women		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age:	70.1±0.5yr		Cases: Men and women aged ≥ 60yr who participated in phase III NHANES (1991-94); available tHcy measured levels	Cases: < 8 yr follow-up; Hx of stroke; unable to learn the word: "apple, table, and penny" in one try; subjects who had asked for the tests to be administered in a language different from that reportedly spoken at home	AD:
	Comparative	%Male:	42				PD:
	Retrospective	Race:	89.2% non-Hispanic white				
Country:	US	Other:	53.7% had smoke previously; 11.8% had been heavy alcohol users at one time; 36% had taken vitamins, minerals within 24h of the interview, 12.6% had high BP, 38.1% had a household income<US$ 20,000/yr		Controls:	Controls:	VascDz:
Setting:	community	Education years, mean	12.3 ±0.2				Other:
Funding:	ND						
Comments:	Characteristics are given for total population not separately for the comparative groups						

Predictor(s): (eg, B vit level)	Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
RBC folate, serum folate	"Apple, table, penny" test	Dichotomous outcome 0, >0	N enrolled:	1270	ND	ND
			N analyzed:	1145	37	1108
			Drop-outs (%):	125	ND	ND
Comments:	RBC folate and serum folate was measured according to standardized protocol					

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		Total	Population of interest	Control
RBC folate, serum folate	Patients in the upper half of the serum folate distribution; patients in the lower half of the serum folate distribution	Paragraph delayed recall test	Continuous scale 0-6	N enrolled:	1200	ND	ND
				N analyzed:	1141	ND	ND
				Drop-outs (%):	59		
Comments:							

Other predictors/outcomes reported:	tHcy, sex; age; years of education; race-ethnicity; pack-years of cigarette smoking; heavy alcohol use; high BP; BP medication use; blood lead concentration; selenium; TCHOL; triacylglycerol; CRE; Fe; total Calcium; β-carotene; Vit A, B12, C, E; household income		
Follow-up duration (if applicable):	N/A		
Reasons for drop out (if applicable):	Demographic data not available		
Limitations:	Unkown whether the population included patients with dementia, etc or not; exact results (β coefficient, etc) not given; inconsistencies between text and table legend (Hcy correlation with serum folate)		
Quality (A/B/C):	C	Applicability (1/2/3):	3

Outcome(s):	Results (Text)
"Apple, table, penny" test	Part of the MMSE (REF 14); the subjects' score on the test is a number from 0 to 3, corresponding to the number of the 3 items successfully recalled after the delay
Paragraph delayed recall test	The test was administered by trained lay interviewers according to a standard protocol (REF 11). All subjects were told that a short story would be read to them, subsequent to which they would be asked to repeat the story back to the interviewer. Then, the interviewer continued with a few additional questions unrelated to the story or to cognitive function. Finally, the subjects were asked to repeat the story a second time. The was scored according to the 6 main story ideas recalled by the subjects after the brief delay. This test is characteristic of a type of test commonly used to evaluate short-term verbal memory (REF 15). Also such tests may be particularly effective at distinguishing between subjects who will and will not progress to a Dx of AD
Paragraph delayed recall test	Patients in the upper half of the serum folate distribution recalled on average >4 of the 6 main ideas of the story; patients in the lower half of the serum folate distribution recalled significantly fewer stories ($p<0.001$)

Correlation of Predictors with Outcomes (cross-sectional studies)

Folate levels in different groups according to paragraph delayed recall test score

Description of (Sub-) Groups	N	Sr folate nmol/L *p*			RBC folate nmol/L *p*			(Sr/CSF) (B vit) (unit)			(Sr/CSF) (B vit) (unit) *p*		
		Mean	SE/SD	r=	Mean	SE/SD	r=	Mean	SE/SD	r=	Mean	SE/SD	r=
Paragraph delayed recall test 0	37	12.3	ND	ND	464	ND	ND						
Paragraph delayed recall test 1	27	13.5	ND	ND	399	ND	ND						
Paragraph delayed recall test 2	82	16.8	ND	ND	433	ND	ND						
Paragraph delayed recall test 3	200	18	ND	ND	545	ND	ND						
Paragraph delayed recall test 4	333	17.6	ND	ND	488	ND	ND						
Paragraph delayed recall test 5	306	18.9	ND	ND	534	ND	ND						
Paragraph delayed recall test 6	158	18.4	ND	ND	545	ND	ND						

Significant relation with recall score and tHcy levels after adjusted for age, sex, race-ethnicity, years of education, and income ($p<0.05$); linear regression model

Folate levels in different groups according to "Apple, table, penny" test score

Description of (Sub-) Groups	N	Sr folate nmol/L *p*			RBC folate nmol/L *p*			(Sr/CSF) (B vit) (unit)			(Sr/CSF) (B vit) (unit) *p*		
		Mean	SE/SD	r=	Mean	SE/SD	r=	Mean	SE/SD	r=	Mean	SE/SD	r=
"Apple, table, penny" test 0	37	14.2	ND	ND	455	ND	ND						
"Apple, table, penny" test >0	1108	17.8	ND	ND	513	ND	ND						

Serum folate concentration interacted significantly with the serum tHcy concentration in relation to story recall but not to word recall

Correlation

Author, Year: Nagga, 2003	**Ref ID**: 2275	**Vitamins**: Folate
Objective:		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age: AD* 75 AD w/CVD* 76 VD* 78 Cognitive impaired 75	69	Cases: Consecutive patients evaluated for dementia from January 1995 – December 1997,	Cases: Current cobalamin and/or folate substitution, subgroup N < 3	AD: ICD-10 criteria
	Comparative	%Male: 37	51			
	Prospective	Race: ND				PD:
Country:	Sweden	Other:		Controls:	Controls:	VascDz:
Setting:	In/out-patient geriatric clinic of university hospital			≥ 60 yr, randomly selected from general population screened for gastritis with gastroscopy, biopsy, & blood samples in fasting state, no MMSE data		Other:
Funding:	Public & private					
Comments:	*Statistical lower age for controls vs population, except mild cognitive impaired subgroup; differential diagnoses by ICD-10 criteria; none treated for dementia at enrollment; no MMSE data for control group					

Predictor(s): (eg, B vit level)	Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Serum folate nmol/l	Dementia	ICD-10	N enrolled:	224	64 (59 VD)	101
			N analyzed:	224		
			Drop-outs (%):	NA		
Comments:						

Fluoroimmunoassay – reference range 75-475 nmol/l

Other predictors/outcomes reported:	
Follow-up duration (if applicable):	
Reasons for drop out (if applicable):	
Limitations: Analyses for nonfasting patient group vs fasting control group	
Quality (A/B/C): C	Applicability (1/2/3): 3

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Sr Folate (unit) Mean	SD	r=	*p*
AD	47	191	75		
AD w/CVD	9	165	89		
Cognitively impaired	8	279	115		<.05
Control	101	ND	ND		

AD & AD w/CVD had lower levels of blood folate vs cognitively impaired

Correlation

Author, Year: Nilsson, 1996	**Ref ID**: 2337	**Vitamins**: B 12, folate
Objective: To determine plasma tHcy and its main determinants sr cobalamin, blood folate, and sr creatinine in dementia patients and in reference population		

Study characteristics		**Population (DAT)**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	75±10	75±7	Cases: Elderly patients with suspected dementia or other organic brain diseases and referred to the psychogeriatric dept in good nutritional status	Cases: Ongoing or those with recently discontinued vit supplementation, or with creatinine >120 μmol L^{-1}, patients on extreme diets	AD:	ND; diagnosed clinically, psychometric tests, rCBF, EEG, CT and MRI in extreme dementia
	Comparative	%Male:	ND	52				
	Prospective	Race:	Probably white				PD:	Unclear
Country:	Sweden	Other:			Controls: Local population invited for participation in the study	Controls: Unwilling or unable to participate, younger than 60 yr, or sr creatinine >120 μmol L^{-1}	VascDz:	Same as AD
Setting:	Academic hospital						Other:	Frontotemporal dementia and other dementia includes alcohol and braintumor
Funding:	University and private non-industry							
Comments:								

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:
Sr cobalamin*	110-650 pmol/L	DAT	ND
Blood folate**	125-500 nmol/L		
Comments:	Radioassay using vit B12/folate Dual RIA kit		

	Total	**Population of interest**	**Control**
N enrolled:	295	68	163
N analyzed:	295	68	163
Drop-outs (%):	0%		

Other predictors/outcomes reported:	THcy; sr creatinine
Follow-up duration (if applicable):	NA
Reasons for drop out (if applicable):	NA
Limitations:	Xs study; all dementia included for correlational analysis; only levels of B12/folate available for DAT. Unclear definition for DAT not specified
Quality (A/B/C): C	Applicability (1/2/3): 2

Outcome(s):	Results (Text)
All dementia	Significant correlations between the levels of vitamin folate and B12, plasma tHcy in both demented and non demented patients in both groups taken together. No data available for DAT alone

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Sr B 12 pmol/L			*p*	Sr folate nmol/L			*p*	(Sr/CSF) (B vit) (unit)			(Sr/CSF) (B vit) (unit)			*p*
		Mean	SD	r=		Mean	SD	r=		Mean	SE/SD	r=	Mean	SE/SD	r=	
DAT	68	245	98	ND		294	132	ND	<0.05							
Controls	163	256	120			353	156									

Correlation

Author, Year: Nilsson, 2003	**Ref ID**: 2343	**Vitamins**: B12, folate
Objective: To evaluate the association of biochemical tests with morbidity, drug therapy, anthropometry, and gender		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS/Longitudinal	Age: M: 84.4 range: 82-95 F: 85.1 range: 82-100		Cases:	Cases:	AD:	According to NINCDS/ARDRA
	Comparative	%Male: 38		Sample from population-based Swedish twin registry: all like-sex (monozygotic and dizygotic) twin pairs aged ≥ 80 with both members still alive during 1991-94 and agreed to give blood samples		PD:	
	Prospective	Race:					
Country:	Sweden	Other:		Controls:	Controls:	VascDz:	
Setting:	community					Other:	Dementia according to DSM-III-R criteria (F00-03)
Funding:	Government (US)						
Comments:	Although study design is for longitudinal study, results for dementia are analyzed as XS (comparison of vit levels among different groups at a certain time-point)						

Predictor(s): (eg, B vit level)	Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
B12	Dementia	DSM-III-R criteria	N enrolled:	535	86	N/A
folate	Dementia	DSM-III-R criteria	N analyzed:	535	86	N/A
			Drop-outs (%):	N/A	N/A	N/A
Comments:	Population (N: 535) also includes people with other morbidities not extracted for the purpose of this project; 256 subjects are reported as having intact cognition but it is not clear whether they are compared to demented sub-group); cases on B12-therapy were excluded; B12, folate: analyzed by time-resolved fluoroimmunoassay using an AutoDelfia instrument (Wallac); normal values for B12: 284 pmol/L and folate: 10.5 pmol/L						

Other predictors/outcomes reported:	Albumin, calcium, TCHOL, HDL, -GT, potassium, sodium, urea, urate, CRE, free T4, TSH, homocysteine, BMI, waist circumference

Follow-up duration (if applicable):	N/A		
Reasons for drop out (if applicable):	N/A		
Limitations:	High number of comparisons may lead to significant results by chance; results at a significance level <0.001 should be interpreted with caution; results and discussion are mixed together with not much clarity		
Quality (A/B/C):	C	Applicability (1/2/3):	2

Outcome(s):	Results (Text)
Dementia	Folate was significantly lower in women with dementia ($p<0.005$); NS differences for B12

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	(Sr) (B 12) (pmol/L) *p*			(Sr) (folate) (pmol/L) *p*			(Sr/CSF) (B vit) (unit)			(Sr/CSF) (B vit) (unit) *p*		
		Mean	SE/SD	r=	Mean	SE/SD	r=	Mean	SE/SD	r=	Mean	SE/SD	r=
Male with dementia (Dx before 1995)	20	215			9.3								
Male with intact cognition	83	313			10.8								
Female with dementia (Dx before 1995)	66	257			8.1		<0.005						
Female with intact cognition	173	297			10.5								

Correlation

Author, Year: Postiglione, 2001	**Ref ID**: 2583	**Vitamins**: Folate, B12
Objective: Correlate B vitamins to AD and MTHFR gene		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	Case-control	Age: 68		Cases: AD, living at home, able to eat unaided	Cases: Vascular dementia. Institutionalized or hospitalized in previous 3 mo. Vitamin supplementation, substances affecting homocysteine metabolism.	AD:	DSM-IV, NINCDS-ADRDA
	Comparative	%Male: 39%				PD:	
	Retrospective	Race: nd					
Country:	Italy	Other:		Controls:	Controls:	VascDz:	NINDS-AIREN
Setting:	Memory clinic			No dementia. MMSE>27. Mostly from among those who accompanied cases.	Disease affecting homocysteine metabolism.	Other:	
Funding:	nd						
Comments:							

Predictor(s): (eg, B vit level)		Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
Plasma folate*	ng/mL & nmol/L	AD diagnosis	N enrolled:		74	74
Plasma B12**	pg/mL & pmol/L		N analyzed:		74	74
C677T MTHFR mutation***			Drop-outs (%):			
Comments:						

* IMX system (Abbott). Normal range 3.1-12.4 ng/mL
** IMX system (Abbott). Normal range 179-1132 pg/mL
*** PCR

Other predictors/outcomes reported:	Homocysteine		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:			
Quality (A/B/C):	B	Applicability (1/2/3):	2

Outcome(s):	Results (Text)
Interaction of B12 or Folate and MTHFR	No significant differences in B12 or Folate levels by subcategories of cases or controls who were homozygous for MTHFR C677T or non-homozygous
Interaction of B12 and Folate with AD duration	Statistically significant correlation between duration of disease (months) and plasma folates ($r = –0.580$, $P<0.05$) and B12 ($r = –0.460$, $P<0.05$). Thus a decrease in B vitamin levels with AD duration.

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Plasma B12 pmol/L Mean	SD	p UNADJ	Plasma Folate nmol/L Mean	SD	p UNADJ	Plasma B12 pmol/L Mean	SD	p ADJ*	Plasma Folate nmol/L Mean	SD	p ADJ*
AD	74	491	144	<.001	5.7	2.1	<.001	689	301	NS	8.9	3.3	NS
Healthy	74	780	211		8.5	3.2		701	234		7.8	3.7	
AD	74	4/74 (5%) < 179 pg/mL		nd	15/74 (20%) < 3.1 ng/mL		nd						
Healthy	74	0%			0%								

* Adjusted for age, serum creatinine, and duration of AD

Correlation

Author, Year: Quadri, 2004	**Ref ID**: 2604	**Vitamins**: Folate, vit B12
Objective: To examine the associations of plasma tHcy, sr folate, vit B12 concentration with mild cognitive impairment, AD, VascDz, and to inquire into the relationships between the biochemical variables and neuroradiologic mechanisms		

Study characteristics		**Population: AD**		**Cog impaired**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	79.1±7.7	76.1±7.1	75.6±8.5	Cases: consecutive subjects from the memory clinic with dementia and Cog impaired	Cases: Younger than 60 yr, with an isolated cognitive deficit, affected by dementias other than AD or VaD, or whose plasma tHcy conc not available, or those with vit B12 >600 pmol/L, folate >30 nmol/L or serum creatinine >180 μmol/L	AD:	NINCDS-ADRDA and CERAD for probable or possible AD
	Non-Comparative	%Male:	34.3	40.7	38.2				
	Prospective	Race:	Probably 100% W	Probably 100% W	Probably 100% W			PD:	NA
Country:	Switzerland	Other: Alcohol intake % >drinks/d	0	1.2	1.8	Controls:	Controls:	VascDz:	Based on CERAD criteria
Setting:	Hospital clinic	Education	7.9 ±2.5	9.1 ±3.6	9.9 ±3.8	elderly controls free of cognitive impairment	ND	Other:	Cognitively impaired0.5 level on the clinical dementia rating scale
Funding:	ND								
Comments:	NINCDS-ADRDA and CERAD: National Institute of Neurological and Communicative Disorders-Alzheimers Disease and Related Disorders Association and of the Consortium to Establish a Registry for Alzheimers disease for possible AD								

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		Total	Population of interest		Control
Serum vit B12*	ND	MMSE	0-30	N enrolled:	210	AD=74	Cog Impair=81	55
Serum folate**	ND	Minimum medial temporal thickness	mm	N analyzed:	210	74	81	55
				Drop-outs (%):	0%			
Comments:								

* B12 measured with a radioimmunoassay kit with the use of ^{125}I and for folate with ^{57}Co: normal range not specified

Other predictors/outcomes reported:	Plasma tHcy		
Follow-up duration (if applicable):	NA		
Reasons for drop out (if applicable):	--		
Limitations:	Cross-sectional study; reference range for vitamins not available		
Quality (A/B/C):	B	Applicability (1/2/3):	3

Outcome(s):	Results (Text)
CT appearance of white matter lesions	NS association with lower folate or vit B12 concentration in the demented group or in the whole sample

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Sr folate nmol/L			p	Sr B12 pmol/L			p	CT scan Min medial temporal lobe thickness mm			p
		Mean	SD	r=		Mean	SD	r=		Mean	SD	r=	
AD	74	13.6	5.6		0.04	281	111		NS	12.2	2.6		NS
CDR 0.5	81	14.0	5.9		0.04	275	117		NS	13.7	3.0		NS
Control	55	16.9	5.8			278	99			14.5	1.9		

Description of (Sub-) Groups	N	Among CDR 0.5				N	AD patients			
		OR (Adj 1*)		OR (Adj 2*)			OR (Adj 1*)		OR (Adj 2*)	
Vit B12 (Reference gp) >303 pmol/L	81	1		1		74	1		1	
Vit B12 234-303 pmol/L		0.8	(0.3, 2.0)	0.8	0.3, 2.0		0.6	0.2, 1.7	0.3	0.1, 1.1
Vit B12 <234 pmol/L		1.0	(0.4, 2.4)	0.7	0.3, 1.8		0.8	0.3, 2.0	0.7	0.4, 1.2
Sr folate (Reference gp) >19.5 nmol/L	81	1		1		74	1		1	

Sr folate 13.5-19.5 nmol/L		1.0	0.4, 2.8	0.9	0.3, 2.6		2.1	0.7, 6.4	2.1	0.6, 6.8
Sr folate <13.5 nmol/L		3.4	1.3, 8.7	3.1	1.2, 8.1		3.7	1.3, 10.7	3.5	1.1, 11.2

* Adj 1, adjusted for for age, gender, education and creatinine …
Adj 2*) age, gender, education and creatinine, Hcy, vit B12 and folate

Correlation

Author, Year: Ravaglia, 2000	**Ref ID**: 2642	**Vitamins**: B12, folate, B6 (extracted)
Objective: To study the association between cognitive status and plasma tHcy levels in centenarians		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	~100	N/A	Cases: **Centenarian** residents in 2 Provinces (Ravenna and Bologna), who underwent a standardized assessment for cognitive function, from Jan 1994 to Jan 1995	Cases: Blood specimens not available	AD:	Clinical Dx (McKahn et al, 1984)
	Comparative	%Male:	32	N/A			PD:	ND
	Prospective	Race:	ND	N/A				
Country:	Italy	Other:			Controls: N/A	Controls: N/A	VascDz:	WHO, 1992
Setting:	community						Other:	Cognitively impaired-not demented: (Dementia as defined by DSM IV criteria, APA 1994
Funding:	government							
Comments:	13 participants had no cognitive problem							

Predictor(s): (eg, B vit level)	Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
B6 level	AD	N enrolled:	66	34	N/A
B6 level	Cognitively impaired-not demented	N analyzed:	ND	10	N/A
B6 level	Normal cognitive status	Drop-outs (%):	N/A	13	N/A
Comments:	B6 measured by HPLC (for pyridoxal-5'-phosphate: active coenzyme form of B6); lower reference value for plasma B6: 11.7 nmol/L				

Other predictors/outcomes reported: serum Cre; serum folate; serum B12; plasma tHcy	
Follow-up duration (if applicable): N/A	
Reasons for drop out (if applicable): N/A	
Limitations: power calculations not measured; results not reported	
Quality (A/B/C): C	Applicability (1/2/3): 1

Outcome(s):	Results (Text)
B6 deficiency	B6 deficiency was present in 85% of normal centenarians, 50% of cognitively impaired not-demented, and 64.7% of AD. Among VascDz patients 40% had B6 deficiency; Among the 3 patients with other dementia (PD, alcoholism, and hypothyroidism) 1 had B6 deficiency
Cognitive status (AD, Cognitively impaired-not demented, Normal)	NS difference among the groups was found for B6 (ANOVA followed by multiple comparisons Tukey test, F:0.734, p=0.485)

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	**N**	**(Sr) (B 6) (nmol/L) *p***	**(Sr/CSF) (B vit) (unit) *p***	**(Sr/CSF) (B vit) (unit)**	**(Sr/CSF) (B vit) (unit) *p***
		Mean SE/SD r=	**Mean SE/SD r=**	**Mean SE/SD r=**	**Mean SE/SD r=**
AD	34	9.8			
Cognitively impaired-not demented	10	11.9			
Normal cognitive status	13	8.1			

B6 measured by HPLC (for pyridoxal-5'-phosphate: active coenzyme form of B6); lower reference value for plasma B6: 11.7 nmol/L

Correlation

Author, Year: Ravaglia, 2003	**Ref ID**: 2644	**Vitamins**: Folate, B12
Objective:		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age: MMSE 24-25 78.6 26-28 73.1 >28 71.8	NA	Cases: All residents of Conselice Municipality (Ravenna Province), ≥65yr, MMSE ≥ 24	Cases: medical condition or drug tx affecting tHcy concentrations: hx AMI, stroke/transient ischemic attacks, liver disease, reduced renal excretion, cancer, vitamin tx, theophylline tx, psychotropic drugs, cytotoxic drugs, HRT; cognitive impairment: epilepsy, psychiatric illness, sensory-motor impairments affecting neuropsychological testing, clock drawing test score ≤ 6, one or more ADL	AD:
	Comparative	%Male: 45	NA			
	Prospective	Race: ND	NA			PD:
Country:	Italy	Other:		Controls:	Controls:	VascDz:
Setting:	Community					Other:
Funding:	Government					
Comments:	Subjects had clinical exam, MMSE, & interview for lifestyle, medication use, medical history, sociodemographic, dietary information.					

Predictor(s): (eg, B vit level)	Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Serum folate*	MMSE	30 pt Italian version	N enrolled:	650		
Serum vitamin B12*	MMSE	30 pt Italian version	N analyzed:	650		
			Drop-outs (%):	NA		
Comments:						

*Immunoelectrochemiluminescence analysis – Elecsys Folate Immunoassay & Elecsys B12 Immunoassay for Elecsys 2010 System; lower reference values 5.7 nmol/L for serum folate and 148 pmol/L vit B12

Other predictors/outcomes reported:	Predictor serum creatinine significantly higher in MMSE score 24-25 than score >28, Plasma tHcy significantly higher in group with MMSE 26-28 than MMSE > 28 & group MMSE 24-25 higher than MMSE 26-28; trend for increase physical activity to increase MMSE scores
Follow-up duration (if applicable):	
Reasons for drop out (if applicable):	
Limitations:	
Quality (A/B/C): C	Applicability (1/2/3): 2

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Sr	B 12	(unit)	*p*	Sr	Folate	unit	*p*
		Mean	95%CI	r=		Mean	95% CI	r=	
MMSE 24-25	46	233	206 – 264	NA		11.4	10.0 – 13.0	NA	
MMSE 26-28	259	240	228 – 253		NS	11.3	10.7 – 11.9		NS
MMSE >28	345	237	227 – 248			11.6	11.1 – 12.2		

Correlation

Author, Year: Ravaglia, 2004	**Ref ID**: 2646	**Vitamins**: B12, folate, B6 (extracted)
Objective: To study the association between specific cognitive skills and plasma tHcy levels in healthy and cognitively normal elderly community dwellers and to analyze several potential confounders of tHcy levels		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Cohort	Age: 72.9 +/-SD 8.2 Range 65-91yr	N/A	Cases:	Cases:	AD:
	Non-comparative	%Male: 53	N/A	All residents of Conselice Municipality (Ravenna Province), aged ≥65yr	Institutionalization; major sensory deficits; epilepsy; major psychiatric illness; infections of the brain; surgical intervebtion for brain tumor or aneurisms; mental retardation; significant developmental learning disorders; focal brain lesions; alcoholism; head trauma with loss of consciousness >1h; GDS ≥20; dementia; loss of dependence in IADL due to cognitive impairment; Hx acute MI, stroke or TIA; current liver disease; reduced renal excretion (Cre serum>133µmole/L); cancer; DM; Tx with Vit, theophylline, psychotropic drugs, cytotoxic drugs, and ERT	PD:
	Retrospective	Race: ND	N/A			
Country:	Italy	Other: Education, yr: 4.3 +/- SD 1.5		Controls:	Controls:	VascDz:
Setting:	community			N/A	N/A	Other: Demetnia (used as exclusion criterion) defined by DSM IV, APA 1994
Funding:	ND					
Comments:	Included participants were all non-demented healthy elderly people					

Predictor(s): (eg, B vit level)	Outcome(s):	Definition:		Total	Population of interest	Control
B6	Mental Deterioration Battery (MDB)	7 parts that provide info for different areas of cognition: Reye's 15 word immediate and delayed recall for verbal memory, phonemic word fluency and sentence construction for language, Raven's progressive matrices '47 for logical reasoning, immediate visual memory for visual memory, freehand copying of drawings and landmarks for constructional praxis	N enrolled:	62		N/A
	Prose memory test, IGNSA 1987		N analyzed:	ND		N/A
	Corsi block tapping test, IGNSA 1987	Evaluation of short-term spatial memory	Drop-outs (%):	N/A		N/A
	MMSE	Italian version				
Comments: B6 measured by HPLC (for pyridoxal-5'-phasphate: active coenzyme form of B6)						

Other predictors/outcomes reported:	age; years of education; serum Cre; serum folate; serum B12; plasma tHcy		
Follow-up duration (if applicable):	N/A		
Reasons for drop out (if applicable):	N/A		
Limitations:	non-controlled study; power calculations not measured; results not reported		
Quality (A/B/C):	C	Applicability (1/2/3):	1 (healthy elderly who live in a small community in Italy)

Outcome(s):	Results (Text)
Neuropsycologiacal measures	NS association between B6 levels and neuropsycologiacal measures (specific results not given)

Correlation

Author, Year: Refsum, 2003	**Ref ID**: 2661	**Vitamins**: B12
Objective: Evaluation of holotranscobalamin in cognitively impaired		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age:	75.2 (72.8-77.7)	70.5 (68.4-72.7)	Cases: Varying degrees of cognitive dysfunction, referred to Oxford Project to Investigate Memory and Ageing. Histologically confirmed at autopsy. Serum available for re-testing	Cases: Age <55 y, no blood sample available (original criteria)	AD: CERAD criteria
	Comparative	%Male:	43%	32%			
	Retrospective	Race:	nd	nd			PD:
Country:	UK	CAMCOG:	39.3 (33.9-44.8)	100.4 (95.6-105.2)	Controls:	Controls:	VascDz:
Setting:	Clinic	MMSE	11.4 (9.8-13.0)	28.9 (27.5-30.3)	Elderly volunteer controls without symptoms of memory impairment (some of whom were patients' relatives). Serum available for re-testing		Other:
Funding:	Pharmaceutical						
Comments:	**SUBSET OF CLARKE 1998 REF ID 622**. Later re-evaluation of same subjects.						

CAMCOG, Cambridge Cognitive Examination, maximum score 107
MMSE, Mini-Mental Status Examination, maximum score 30

Predictor(s): (eg, B vit level)	Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
Holotranscobalamin (holoTC)* pmol/L	AD diagnosis	N enrolled:	116	51	65
metabolically active fraction of plasma cobalamins		N analyzed:	116	51	65
		Drop-outs (%):			
Comments:					

* Axis-Shield, solid phase RIA. Normal range determined as part of study.

Other predictors/outcomes reported:	Serum cobalamin (total), (Serum folate: see Clarke 622)		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:			
Quality (A/B/C):	C	Applicability (1/2/3):	2

Outcome(s):	Results (Text)

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	**N**	**Serum**	**HoloTC**	**(pmol/L)**	***p***			
		Geometric Mean	**Range**	**r=**				
AD (histology)	51	41.1	(36.1-46.8)		<0.001			
Controls	65	57.1	(51.1-64.1)					
ALL		**OR (Adj 1*)**		**OR (Adj 2*)**				
Low holoTC (<40 pmol/L)	116	3.40	(1.45-7.97)	2.82	(1.02-7.83)			
HIGH Hcy (>14 µmol/L)								
Low holoTC (<40 pmol/L)	~58	9.45	(2.31-38.7)					
LOW Hcy (<14 µmol/L)								
Low holoTC (<40 pmol/L)	~58	0.91	(0.15-5.31)					

* Adj 1, adjusted for age and sex, and **total cobalamin**, MMA, Hcy, and Folate; Adj 2, adjusted for age, sex, smoking, social class, and ApoE ε4, and **total cobalamin**, MMA, Hcy, and Folate.

Correlation

Author, Year: Regland, 1988	**Ref ID**: 2663	**Vitamins**: B12, folate
Objective:		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age:		72	Cases:	Cases: ND	AD: DSM-III
		AD	59				
		Senile dementia	75				
	Comparative	%Male:	ND	ND	Hospital geropsychiatric unit dementia patients		
	Retrospective	Race:	ND	ND			PD:
Country:	Sweden	Other:			Controls:	Controls:	VascDz:
Setting:	Inpatient geropsychiatric unit				Hospital geropsychiatric unit dementia patients diagnosed with vascular dementia		Other:
Funding:	Government grant & private foundations						
Comments:	66 yr cut-point for AD vs senile dementia of AD type						

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Serum B12	pmol/l	Dementia	DSM-III criteria	N enrolled:	145	91	54
Blood folate	nmol/l			N analyzed:	145	91	54
Plasma folate	nmol/l			Drop-outs (%):			
Comments: Medication and nutrition history unavailable for analyses							

Isotope dilution assay
Reference limit for blood folate 90-450 nmol/l

Other predictors/outcomes reported: Stratification of total group by serum B12 levels at 200 pmol/l resulted in patients with low B12 were older and blood folate was lower than normal B12 level; negative correlation between serum B12 levels and platelet MAO activity ($r = -0.33$, $p < 0.002$), negative correlation for HVA and vitamin B12 ($r = -0.23$, $p < 0.02$)		
Follow-up duration (if applicable):		
Reasons for drop out (if applicable):		
Limitations:		
Quality (A/B/C):	B	Applicability (1/2/3): 1

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Serum B12 (unit)			p	Plasma Folate (unit)			p	Blood Folate (unit)			p
		Mean	SD	r=		Mean	SD	r=		Mean	SD	r=	
Control	54	335	184		0.0002	13	8		NS	277	144		NS
AD	35	319	132			11	4			262	77		
Senile dementia	56	246	158			12	5			244	84		

Serum vitamin B12: Control > Senile dementia, AD > Senile dementia
Mean vitamin B12 concentrations levels for control & AD groups were normal vs low concentration for senile dementia group

Correlation

Author, Year: Religa, 2003	**Ref ID**: 2678	**Vitamins**: B12, folate
Objective: To examine the relationship between plasma Hcy levels and vit status and to identify the genetic status of the ApoE and MTHFR gene polymorphism in Polish AD, mild cognitive impairment and age matched controls		

Study characteristics		**Population AD**	**MCI**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age: 74.2(6.3)	70.7(7.0)	71.2 (6)	Cases: AD patients from the Alzheimer day clinic by examination clinical and radiological	Cases:	AD:	Meeting the criteria of NINCDS_ADRDA fro probable AD and also DSM-IV
	Comparative	%Male: ND	ND	ND				
	Prospective	Race: ND	ND	ND			PD:	
Country:	Poland	Other:			Controls: MCI patients from the clinic and examined by a panel of specialists and neurologists	Controls: Cognitively intact patients from surgical and medical wards or spouses of AD patients	VascDz:	
Setting:	Academic medical						Other:	
Funding:	Gov and Foreign grants						Mildly cognitive impaired	Clinical dementia rating scores of 0.5 and global deterioration scale scores of 3 and presented with memory complaints but not severe enough to fit in dementia criteria
Comments:	Cognitively intact healthy adults based on MMSE score MMSE: 29(+/-1) normal							

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Folic acid	5.3-14.4 ng/ml	Classification of study population based on clinical dementia rating score and other clinical symptoms and MMSE	MMSE: 29(+/-1) normal	N enrolled:	297	99	98 MCI+100 healthy
Vit B12	157-1059 pg/mL			N analyzed:	297	99	198
				Drop-outs (%):	na		
Comments:	Folate by AxSYM folate reagent assay and vit B12 by immunoassay; Normal ranges in the table						

Other predictors/outcomes reported:	MTHFR gene polymorphism; ApoE; homocysteine

Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	No adjustment of cross-sectional data		
Quality (A/B/C):	C	Applicability (1/2/3):	3

Outcome(s):	Results (Text)
tHcy	The mean plasma tHCy levels were sig higher in patients with AD (18.03±10.8) than in controls (14.43±4.48;p<0.0001) and MCI (14.15±4.09; p<0.0001).
Apo E 4 allele	The distribution of ApoE4 allele was sig higher in the AD population (p<0.0001) than in controls and MCI (p<0.0001)

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	**N**	**Sr Folate ng/ml**			***p***	**Sr B12 pg/mL**			***p***
		Mean	**SD**	**r=**		**Mean**	**SD**	**r=**	
Probable AD	99	8.5	3.38	NA	NS	316.7	139.5		<0.05*
Mild cognitive impaired (MCI)	98	10.87	3.93	ND	NS	386.3	158.7		NS
Cognitive intact Healthy elderly	100	7.56	5.39			413.5	241.3		

* Compared to Cognitive intact healthy elderly

Correlation

Author, Year: Robins Wahlin, 2001	**Ref ID**: 2741	**Vitamins**: B12, folate
Objective: To provide further evidence of the presence and extent of vitamin-related effects on cognitive performance in old age		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	85.5 (5)	83.9 (	Cases: All 75 yrs and above, and residents living in the Kungsholmen parish in Stockholm, Sweden and were assessed in 2 phases for inclusion. A random sample of those with an MMSE score above 23 were assessed in phase 2 with extensive examinations	Cases: All demented subjects, psychiatric patients or with psychiatric diagnosis, visual disabilities, not screened for vit B12, folate status, on vitamin supplement meds, and those who did not complete the cognitive tests. Subjects with intake of anticonvulsants, anti-metabolites, and trimethoprim and other anti-folate meds	AD:	NA
	Comparative	%Male:	18%	21%			PD:	NA
	Prospective	Race:	Probably white 100%	Probably white 100%				
Country:	Sweden	Other:			Controls: Same as above, the controls were selected from those with normal B12 and folate	Controls: Same as above	VascDz:	NA
Setting:	Community						Other:	
Funding:	Gov, private, non-industry (multiple sources)						Subjects were categorized according to the vitamin status	
Comments:	Subjects were grouped into vitB12 and/or Folate deficient and controls were both vit B12 and folate normal							

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		Total	Population of interest	Control
Vit B12 blood level	200 pmol/L	Clock setting and reading	Drawing and reading clock times with clock faces with marks at number location and no numbers marked	N enrolled:	230	104	126
Folate blood level	11 nmol/L	Trail making test A and B, accuracy	A shortened version of the TMT from the Halstead Reitan Battery; part A had a max score of 12 and part B had a max score of 11. Accuracy and number of seconds needed to finish each part were registered with unlimited performance time	N analyzed:	230	104	126
		Trail making test A and B, time		Drop-outs (%):	0%		
		Digit span forward and backward	Administered using WAIS-R criteria				
		Verbal fluency tests					
Comments:	Analyzed with ANOVA and regression analysis Vit B12 and folate assessed using radioimmunoassay method with cut-offs 200 pmol/L and 11 nmol/L respectively						

Other predictors/outcomes reported:	MMSE		
Follow-up duration (if applicable):	NA		
Reasons for drop out (if applicable):	NA		
Limitations:			
Quality (A/B/C):	B	Applicability (1/2/3):	3

Outcome(s):	Results (Text)
Clock test	No significant main or interaction effects
Block design*	Main effects of B12, F (1,226)=5.33, MSE=40.96, P<0.05, ω2=0.02; groups with lower levels of vit B 12 performed worse than the groups with normal vitamin levels Main effects of folate, F (1,226)=24.85, MSE=40.96, P<0.0005, ω2=008; groups with lower of vit folate performed worse than the groups with normal vitamin levels Significant association between B12 and Block design performance (paced: beta=0.19; P<0.01; self-paced: beta=0.15, P<0.05)
Trail making test A	No reliable effects either accuracy or time
Trail making test B	Significant main effects of FA on accuracy, F (1,226)=9.13, MSE=7.07, P<0.01, ω2=0.03 Significant main effects of FA on time, F (1,226)=7.68, MSE=11 114.19, P<0.01, ω2=0.03 The low folate values were associated with lower performance The effect of B12 and the interaction effect were not significant
Digit span forward*	No reliable or interaction effects
Digit span backward*	Significant main effects of FA on accuracy, F (1,226)=8.47, MSE=1.05, P<0.01, ω2=0.03 The low folate values were associated with lower performance The effect of B12 and the interaction effect were not significant
Verbal fluency test	Significant effects for both B12 P<0.01and folate P<0.05

* Part of Wechsler Adult Intelligence Scale

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	N B12/N folate		*p*	N	L B12/N folate		*p*	N B12/L Folate		*P*	L B12/L folate		*p*
		Mean	SD			Mean	SD		Mean	SD		Mean	SD	
MMSE	126	27.46	2.22	Nd		26.5	2.76	nd	26.26	2.26	nd	25.64	2.56	nd

Correlation

Author, Year: Scileppi, 1984	**Ref ID**: 10016	**Vitamins**: B1, B2, B6, B12, Folate
Objective: Compare vitamin levels in AD v non-AD		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age: nd		Cases: Series of subjects coming to a subspecialty dementia clinic in a prosperous suburb. Diagnosed with AD.	Cases:	AD: nd
	Comparative	%Male: nd				PD:
	Prospective	Race: nd				
Country:	US	Other:		Controls: Same as cases, except diagnosed with condition other than AD (implied only). Controls = Normal (intellectually intact, n=10), Multi-infarct dementia (n=28), Other dementias (n=8), and Depression (n=12)	Controls:	VascDz:
Setting:	Dementia clinic					Other:
Funding:	Industry, Non-Profit					
Comments:						

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Blood B1*	ng/mL	Dx of AD v Control	nd	N enrolled:	113	55	58
Blood B2**	ng/mL			N analyzed:		54-55	58
Blood B6***	ng/mL						
Blood B12****	pg/mL						
Blood folate*****	ng/mL			Drop-outs (%):			
Comments:							

* Analyzed protozoologically. Lower level of normal = 25 ng/mL
** Analyzed protozoologically. Lower level of normal = 110 ng/mL
*** Analyzed protozoologically. Lower level of normal = 29 ng/mL
**** Analyzed protozoologically. Lower level of normal = 105 pg/mL
***** Analyzed with Lactobacillus casei. Lower level of normal = 5.0 ng/mL

Other predictors/outcomes reported:	Other vitamins		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Very limited reporting		
Quality (A/B/C):	C	Applicability (1/2/3):	2

Outcome(s):	Results (Text)

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Bl B1 ng/mL			N	Bl B2 ng/mL			N	Bl B6 ng/mL			N	Bl B12 pg/mL			N	Bl Folate pg/mL		
		Mean	SEM	*P*		Mean	SEM	*P*		Mean	SEM	*P*		Mean	SEM	*P*		Mean	SEM	*P*
AD	55	46	4	NS	55	295	10	NS	54	44.9	6.3	NS	55	290	31	NS	55	11.7	1.5	NS
Control (non-AD)	58	48	4		58	292	9		58	38.2	2.4		58	533	25		58	10.7	1.0	

Univariate analyses.
No explanation for large difference in B12, with relatively small SEM, but NS difference.

Correlation

Author, Year: Serot, 2001	**Ref ID**: 2933	**Vitamins**: B6, B12, Folate
Objective: Evaluation of choroids plexus dysfunction, thus folate levels		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age: 75.9+/-6.6	I. 40.6+/-11.3 II. 72.7+/-7.0	Cases: All CSF samples obtained by lumbar puncture, performed to rule out such neurological diseases as CNS infection, subarachnoid hemorrhage, or for diagnostic myelography. Samples contained <0.06 g/L protein and <3 cells/mL. By review or medical records, divided into 3 groups: III. AD, >60 y	Cases:	AD: NINCDS-ADRDA
	Non-comparative	%Male: 37%	I. 52% II. 28%			
	Retro-spective	Race: nd	nd			PD:
Country:	France	Other:		Controls: I. Normal mentally healthy adults 20-60 y II. Normal, mentally healthy elderly >60 y	Controls:	
Setting:	Mixed					Other:
Funding:	Government, Non-profit					
Comments:						

Predictor(s): (eg, B vit level)	Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
CSF Folate* ng/mL	AD v non-AD	N enrolled:	126	30	I. 60 II. 36
Serum Folate* ng/mL	MMSE	N analyzed:	126	30	I. 60 II. 36
		N analyzed (serum):		30	I. 24 II. 28
Comments:					

* Sanofi Diagnostics Pasteur: Access Immunoassay System. ND on normal values.

Other predictors/outcomes reported:	
Follow-up duration (if applicable):	
Reasons for drop out (if applicable):	
Limitations:	
Quality (A/B/C): C	Applicability (1/2/3): 2

Outcome(s):	Results (Text)
MMSE	In group III (AD), CSF-folate levels varied with the severity of dementia with a "slight correlation" (r=0.35)

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	CSF Folate ng/mL Mean	SD	r=	*p*	N	Serum Folate ng/mL Mean	SD	r=	*p*		
AD (III)	30	8.26	1.82		<0.001	30	5.35	2.15		NS		
Healthy young (I)	60	10.47	1.93		NS	24	5.31	1.73				
Healthy elderly (II)	36	9.96	2.01			28	5.81	2.13				

Correlation

Author, Year: Seshadri, 2002	**Ref ID**: 2936	**Vitamins**: B12, folate, B6
Objective: To examine the relation between plasma tHcy levels and newly diagnosed AD in elderly population-based cohort		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	Longitudinal	Age:	76 ± 6 (range 68-97)	N/A	Cases:	Cases:	AD:	NINCDS/ARDRA
	Non-comparative	%Male:	39	N/A	Subjects enrolled in a dementia-free cohort between 1976-78, who underwent their 20th biennial examination between 1986-90 and had Hcy levels measured	ND		
	Prospective	Race:	ND	N/A			PD:	
Country:	US	Other:			Controls: N/A	Controls: N/A	VascDz: 11	ND
Setting:	community						Other: Non-AD degenerative dementia: 11; other types:6	DSM-IV
Funding:	government							
Comments:	Framingham Study participants							

Predictor(s): (eg, B vit level)	Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
B12, Folate, B6	Dementia	N enrolled:	1092	111	N/A
B12, Folate, B6	AD	N analyzed:	1092	83	N/A
		Drop-outs (%):	0	0	N/A

Comments:
Of the total population N=1092, 85% had measurements for B12, 92% for B6, and 98% for folate; not reported how many of these patients with B12, B6, and folate measurements developed dementia and/ or AD
Plasma folate was measured by amicrobial (Lactobacillus casei) assay with a 96-well plate and manganese supplementation
Plasma B12 levels were estimated with the use of a radioassay kit (Magic, Ciba-Corning, Medfield, Mass)
B6 (PLP) was measured by the tyrosine decarboxylase apoenzyme method (REF 32)
Coefficients of variation for these assays were 13% for plasma folate, 7% for B12, and 16% for PLP

Other predictors/outcomes reported: Age, gender, APOE genotype, Hcy levels, education level, cigarette smoking, alcohol intake, DM, SBP, BMI

Follow-up duration (if applicable):	Median 8 yr (range 1-13)		
Reasons for drop out (if applicable):			
Limitations:	Race info not given; results for B12, B6, and folate and their relation to AD /dementia not reported		
Quality (A/B/C):	B	Applicability (1/2/3):	3

Outcome(s):	Results (Text)
Dementia, AD	After adjusting for age, sex, and APOE genotype **none** of the Vit levels (B12, folate, B6) were independently related to the risk of dementia or AD

Correlation

Author, Year: Shahar, 2001	**Ref ID**: 2940	**Vitamins**: Vit B12
Objective: To determine the prevalence of low and low normal vitamin B12 levels in "sick" elderly subjects hospitalized in a geriatric medical center and analyzed the relationship of vitamin B12 levels to several clinical parameters		

Study characteristics		**Population***		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age:	78 (8)		Cases:	Cases:	AD:
	Non-comparative	%Male:	46%		Patients of either gender who were ≥65 yrs old and were discharged from the hospital or died in the hospital between Jan 1 and Dec 31 1996 and included those who had sr vit B12 analyzed once during hospital stay and whose last name commenced with one of the first 12 letters of the Hebrew alphabet	As inclusion criteria	PD:
	Retrospective	Race:	Probably white				
Country:	Israel	Other:			Controls:	Controls:	VascDz:
Setting:	Academic hospital	In-hospital death	38.3% males and 35.9% for females		None		Other:
Funding:	ND						Cognitive impairment ND
Comments:	Though comparative in the study none of the comparative groups were eligible as controls for this data extraction						

* Data available for men and women separately

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest (cog impaired)**	**Control**
Vitamin B12 levels-low	<150 pmol/L	Cognitive impairment	ND	N enrolled:	640	37.2%	
Vitamin B12 levels-borderline	150-250 pmol/L			N analyzed:	640	37.2%	
Vitamin B12 levels-normal	>250 pmol/L			Drop-outs (%):	0		
Comments:							

Sr B12 measured by "access" immunoassay system

Other predictors/outcomes reported:	Folic acid levels correlating with vit B12 levels (not data extracted as no separate subgroup analysis available); % treated for vitamin deficiency		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Poor sampling; no definition of cognitive impairment;		
Quality (A/B/C):	C	Applicability (1/2/3):	1

Outcome(s):	Results (Text)

Correlation of Predictors with Outcomes (cross-sectional studies)-Among cognitive impaired only for this study

Description of (Sub-) Groups Cognitive impairment	**N**	**Sr**	**B 12 vit**	**pmol/L**	***p***
		Mean	**SE/SD**	**%**	
Low B12 <150 pmol/L				46.9%	
Borderline B12 150 to 250				36.4%	
Normal >250				35.7%	
Total cognitive impaired	238				Unadjusted P=NS Adjusted P=0.04

Correlation

Author, Year: Snowdon, 2000	**Ref ID**: 3059	**Vitamins**: Folate
Objective: To investigate the relation between serum folate and the severity of atrophy of the neocortex at autopsy; to investiaget if low serum folate would have a strong association with atrophy of the nerocortex with an atrophic disease process like AD.		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	91 y (died)		Cases:	Cases:	AD:	Neuropathology definitions: neurofibrillary tangle, senile plaques and neuritic plaques per mm^2 microscopic field
	Comparative	%Male:	0		30 nuns who died 2 to 55 mo (average 24 mo) after serum folate measurements were taken.			
	Retrospective	Race:	white				PD:	
Country:	US	Other:			Controls:	Controls:	VascDz:	
Setting:	convent				65 survivors		Other:	
Funding:	National Institute on Aging, Abercrombie Foundation & the Kleberg Foundation							
Comments:								

Predictor(s): (eg, B vit level)	Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
Folate	Neocortex Atrophy	N enrolled:	30	30	
Vitamin B-12	Number of AD lesions	N analyzed:	30	30	
Vitamin B-6		Drop-outs (%):	0	0	
Thiamine					
Comments: only histopathological diagnoses of AD reported in this study; no clinical correlation					

Other predictors/outcomes reported:			
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:			
Quality (A/B/C):	B	Applicability (1/2/3): 3	1

Outcome(s):	Results (Text)
	Among all 30 participants, the age-adjusted correlation of serum folate with the severity of atrophy was –0.40 (p=0.03).
	Among the subset of 15 subjects with significant number of AD lesions, the age-adjusted correlation between folate and the severity of atrophy was –0.80 (p=0.0006). None of the other nutrients were significantly correlated with the severity of atrophy of the neocortex.
	The severity of atrophy of the neocortex was significantly correlated with the mean number of neurofibrillary tangles in the subset of pts with signficant number of AD lesions (r=0.54, p=0.048). Serum folate was not significantly correlated with the mean number of neurofibrillary tangles in the neocortex (r= –0.14, p=0.63).
	Regression analyses for the subset of 12 subjects indicated that folate had a signficant inverse association with cognitive function after adjustment for age and the number of neurofibrillary tangles: a 10-nmol/L decrease in serum folate was associated with a 1-point decrease in the score for the MMSE (p=0.04).

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	**N**	**Sr folate nmol/L**			***p***	**Sr B-12 nmol/L**			***p***	**Sr B-6 nmol/L**				**Sr Thiamine nmol/L**			***p***
		Mean	**SD**	**r=**		**Mean**	**SD**	**r=**		**Mean**	**SD**	**r=**		**Mean**	**SD**	**r=**	
(+) Significant number of AD lesions	15	45	52	–0.80	<0.001	119	58	-.19	NS	319	189	–0.38	NS	142	36	–0.49	NS
Without signficant number of AD lesions	15	61	54	.14	NS	128	94	-.08	NS	290	65	.03	NS	148	30	.05	NS

Correlation

Author, Year: Stewart, 2002	**Ref ID**: 3133	**Vitamins**: Plasma homocysteine
Objective: To investigate the association between homocysteine concentrations and cognitive impairment in an older African-Caribbean population		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age: 65 (n=238?)		Cases: 248 participants with plasma homocysteine data and born in a Caribbean nation	Cases:	AD:
	Comparative	%Male: 47% (n=238?)				PD:
	Retrospective	Race: African/Caribbean descent				
Country:	UK	Other:		Controls:	Controls:	VascDz:
Setting:	Primary care services					Other:
Funding:	Wellcome Trust					
Comments:	Discrepancy between n=238 in table 1 and text description of n=248					

Predictor(s): (eg, B vit level)	Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Highest quartile of homocysteine concentration (>13.85 micromol/L)	Cognitive impairment	Yes or No	N enrolled:	248		
			N analyzed:	248		
			Drop-outs (%):			
Comments: 11 psychometric tests drawn from the Consortium to Establish a Registry for Alzheimer's Disease and WHO batteries; subjects were categorized as having relative cognitive impairment on the basis of scores <30%tile on 6 or more tests, or <10%tile on 4 or more tests.						

Other predictors/outcomes reported:			
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:			
Quality (A/B/C):	B	Applicability (1/2/3): 2	2

Outcome(s):	Results (Text)

	Cognitive impairment was classified in 68 (27%) participants. Raised homocysteine (highest quartile: >13.85 micromol/L) was associated with cognitive impairment (OR=2.50, 95% CI = 1.33 to 4.69). This association persisted after adjustment for age, occupation, other measures of vascular risk, folate, BMI and waist:hip ratio (OR=3.00, 95% CI = 1.35 to 6.69). As with other risk factors for vascular disease in this sample, the association was significant only in those with less education (p-value for interaction=.049). This association was independent of other measures of vascular risk and was not explained by folate concentrations.

Description of (Sub-) Groups	**N**	**Cognitive impairment**	
		OR	**OR (Adjusted for age, occupation, other measures of vascular risk, folate, BMI and waist:hip ratio)**
Homocysteine ≤ 13.85 micromol/L	180 (?)		
Homocysteine >13.85 micromol/L	68	OR=2.50, 95% CI = 1.33 to 4.69	OR=3.00, 95% CI = 1.35 to 6.69

Correlation

Author, Year: Stuerenburg, 2004	**Ref ID**: 3150	**Vitamins**: B12
Objective: To investigate the correlation between plasma B12 levels and cognitive impairment in AD patients		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	71.8 ±SD 8.5	N/A	Cases:	Cases:	AD:	NINCDS/ARDRA criteria (REF 6)
	Comparative	%Male:	45	N/A	Patients with AD	ND		
	Retrospective	Race:					PD:	
Country:	Germany	Other:			Controls:	Controls:	VascDz:	
Setting:	ND				N/A	N/A	Other:	
Funding:	ND							
Comments:								

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
B12		MMSE score	ND	N enrolled:	ND	ND	
B12	Lower percentile (<184ng/mL)	MMSE score	ND	N analyzed:	ND	ND	
B12	Upper percentile (>598ng/mL)	MMSE score	ND	Drop-outs (%):	N/A		
Comments:							

Other predictors/outcomes reported:	age		
Follow-up duration (if applicable):	N/A		
Reasons for drop out (if applicable):	N/A		
Limitations:	sample not well-described; methods of evaluation (B12, MMSE) not described; results not explicitly reported; confounding factors also not considered (except for age)		
Quality (A/B/C):	C	Applicability (1/2/3):	1

Outcome(s):	Results (Text)
MMSE scores	NS correlation between plasma B12 and MMSE scores. A significant inverse correlation became apparent when the MMSE score of those patients with the lowest 10% B12 plasma levels were compared with the upper B12 plasma levels (Spearman rho= -0.36, p=0.008)

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	(Sr) (B 12) (ng/mL)			*p*	(Sr/CSF) (B vit) (unit)			*p*	(Sr/CSF) (B vit) (unit)			(Sr/CSF) (B vit) (unit)			*p*
		Mean	SE/SD	r=		Mean	SE/SD	r=		Mean	SE/SD	r=	Mean	SE/SD	r=	
All subjects (B12 compared to MMSE scores); Spearman rank correlation	241	371	216	ND	0.38											
Subjects with B12<184ng/mL	ND	15.7	6.1	-0.36	0.008											
Subjects with B12>598ng/mL	ND	20	4.6													

Correlation

Author, Year: Teunissen, 2003	**Ref ID**: 3239	**Vitamins**: B12, folate
Objective: To investigate whether elevated serum tHcy is a risk factor for cognitive decline		

Study characteristics		Population	Controls	Inclusion criteria	Exclusion criteria	Definitions
Study design	Longitudinal	Age: 57 ± 11	N/A	Cases:	Cases:	AD:
	Non-comparative	%Male: 59	N/A	Normal aging subjects of MAAS (Maastricht Aging Study) were randomly drawn from the Registration Network Family Practices; baseline medical and neuropsychological examination in 1993;	Evidence of past or present morbidity that may compromise brain function, such as cerebrovascular disease (including stroke), chronic neurological pathology (e.g., dementia, epilepsy or PD), mental retardation or chronic psychotropic drug use	PD:
	Prospective	Race:				
Country:	The Netherlands	Other:		Controls: N/A	Controls: N/A	VascDz:
Setting:	community					Other:
Funding:	Non-profit					
Comments:	For a number of participants (those who did not have available serum sample at baseline) age and gender are not reported					

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		Total	Population of interest	Control
B12, folate	Patients with available B12, folate at baseline	World Learning Test (WLT); Delayed Recall Test	Based upon the Auditory Verbal Learning Test (REF 35); evaluates the ability to acquire and retain verbal info.	N enrolled:	93	93	N/A
B12, folate	Patients with available B12, folate at baseline	Letter-Digit Coding Test (LDCT)	Paper-and-pencil test is a modified version of the Symbol Digit Modalities Test (REF 36) and measures info processing speed.	N analyzed:	92	92	N/A
B12, folate	Patients with available B12 at baseline	STROOP Color-Word Test	Subtask III involves color names but the printing ink is different from the color name. Only the data of subtask III are used in the current study	Drop-outs (%):	1	1	N/A
Comments:	B12, folate were measured using commercial kits (Bayer Immuno 1, Leverkusen, Germany)						

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		Total	Population of interest	Control
B12	Patients with available B12 either at baseline or during follow-up	World Learning Test (WLT); Delayed Recall Test	Based upon the Auditory Verbal Learning Test (REF 35); evaluates the ability to acquire and retain verbal info.	N enrolled:	115	115	N/A
B12	Patients with available B12 either at baseline or during follow-up	Letter-Digit Coding Test (LDCT)	Paper-and-pencil test is a modified version of the Symbol Digit Modalities Test (REF 36) and measures info processing speed.	N analyzed:	114	114	N/A
B12	Patients with available B12 either at baseline or during follow-up	STROOP Color-Word Test	Subtask III involves color names but the printing ink is different from the color name. This test shows robust effects of chronological age (REF 37). Only the data of subtask III are used in the current study	Drop-outs (%):	1	1	N/A
Comments:	B12 were measured using commercial kits (Bayer Immuno 1, Leverkusen, Germany)						

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		Total	Population of interest	Control
folate	Patients with available folate either at baseline or during follow-up	World Learning Test (WLT); Delayed Recall Test	Based upon the Auditory Verbal Learning Test (REF 35); evaluates the ability to acquire and retain verbal info.	N enrolled:	115	115	N/A
folate	Patients with available folate either at baseline or during follow-up	Letter-Digit Coding Test (LDCT)	Paper-and-pencil test is a modified version of the Symbol Digit Modalities Test (REF 36) and measures info processing speed.	N analyzed:	111	111	N/A
folate	Patients with available folate either at baseline or during follow-up	STROOP Color-Word Test	Subtask III involves color names but the printing ink is different from the color name. This test shows robust effects of chronological age (REF 37). Only the data of subtask III are used in the current study	Drop-outs (%):	4	4	N/A
Comments:	Folate was measured using commercial kits (Bayer Immuno 1, Leverkusen, Germany)						

Other predictors/outcomes reported:	Hcy, age, gender, level of eduaction		
Follow-up duration (if applicable):	6 yr		
Reasons for drop out (if applicable):	insufficient serum measurements		
Limitations:	Part of the population not described (age, gender); power calculations not reported		
Quality (A/B/C):	B	Applicability (1/2/3):	3

Outcome(s):	Results (Text)
World Learning Test (WLT); Delayed Recall Test	Based upon the Auditory Verbal Learning Test (REF 35); evaluates the ability to acquire and retain verbal info. The total number of correctly reproduced words on the 5 immediate recall trials is recorded (WLTTOT). After 20 min the subject is asked to reproduce the set of words (Delayed Recall) (REF 31). Higher score reflects better cognitive performance
Letter-Digit Coding Test (LDCT)	Paper-and-pencil test is a modified version of the Symbol Digit Modalities Test (REF 36) and measures info processing speed. The total number of correctly copied corresponding numbers in 90 sec is recorded as test outcome. Higher score reflects better cognitive performance
STROOP Color-Word Test	The test examines the speed at which color names are read (subtask I) and the speed at which color spots are named (subtask II). Subtask III involves color names but the printing ink is different from the color name. The time needed to name the color of the printing ink of the words is recorded. Lower score reflects better cognitive performance. This test shows robust effects of chronological age (REF 37). Only the data of subtask III are used in the current study

Correlation of Predictors with Outcomes (zero order correlation, Spearman correlation coefficients)

STROOP test

Description of (Sub-) Groups	**N**	**(Sr) (B 12) (ng/L) *p***			**(Sr) (folate) (mg/L) *p***			**(Sr/CSF) (B vit) (unit)**			**(Sr/CSF) (B vit) (unit) *p***		
		Mean	**SE/SD**	**r=**	**Mean**	**SE/SD**	**r=**	**Mean**	**SE/SD**	**r=**	**Mean**	**SE/SD**	**r=**
Patients with available B12, folate at baseline	92	406		-0.168 NS	3.9		-0.126 NS						
Patients with available B12 either at baseline or during follow-up	114	396		-0.102 NS									
Patients with available folate either at baseline or during follow-up	111	5		-0.066 NS									

LDCT

Description of (Sub-) Groups	N	(Sr) (B 12) (ng/L)			*p*	(Sr) (folate) (mg/L)			*p*	(Sr/CSF) (B vit) (unit)			(Sr/CSF) (B vit) (unit)			*p*
		Mean	SE/SD	r=		Mean	SE/SD	r=		Mean	SE/SD	r=	Mean	SE/SD	r=	
Patients with available B12, folate at baseline	92	406		0.031	NS	3.9		0.085	NS							
Patients with available B12 either at baseline or during follow-up	114	396		0.081	NS											
Patients with available folate either at baseline or during follow-up	111	5		0.042	NS											

WLTTOT

Description of (Sub-) Groups	N	(Sr) (B 12) (ng/L)			*p*	(Sr) (folate) (mg/L)			*p*	(Sr/CSF) (B vit) (unit)			(Sr/CSF) (B vit) (unit)			*p*
		Mean	SE/SD	r=		Mean	SE/SD	r=		Mean	SE/SD	r=	Mean	SE/SD	r=	
Patients with available B12, folate at baseline	92	406		0.075	NS	3.9		0.037	NS							
Patients with available B12 either at baseline or during follow-up	114	396		-0.008	NS											
Patients with available folate either at baseline or during follow-up	111	5		-0.080	NS											

Delayed recall

Description of (Sub-) Groups	N	(Sr) (B 12) (ng/L)			p	(Sr) (folate) (mg/L)			p	(Sr/CSF) (B vit) (unit)			(Sr/CSF) (B vit) (unit)			p
		Mean	SE/SD	r=		Mean	SE/SD	r=		Mean	SE/SD	r=	Mean	SE/SD	r=	
Patients with available B12, folate at baseline	92	406		0.055	NS	3.9		0.214	<0.05							
Patients with available B12 either at baseline or during follow-up	114	396		0.011	NS											
Patients with available folate either at baseline or during follow-up	111	5		-0.151	NS											

Unstandardized regression coefficients (95%CIs) of B12, folate adjusted for individual baseline age, sex, and educational level

Description of (Sub-) Groups	N	STROOP test		LDCT		WLTTOT		Delayed recall	
		b coefficient (Adj 1*)		b coefficient (Adj 1*)		b coefficient (Adj 1*)		b coefficient (Adj 1*)	
Patients with available B12 at baseline	92	4.24	-22.92, 31.39	-7.66	-17.19, 1.86	0.70	-8.93, 10.33	-0.21	-3.46, 3.04
Patients with available folate at baseline	92	-2.31	-4.98, 0.37	0.54	-0.42, 1.51	0.34	-0.63, 1.3	**0.32****	**0.01, 0.64**
Patients with available B12 either at baseline or during follow-up	114	-0.69	-32.75, 31.37	-3.26	-11.47, 4.95	-1.17	-9.28, 6.93	-0.23	-2.75, 2.29
Patients with available folate either at baseline or during follow-up	111	-0.27	-3.03, 2.5	-0.05	-0.74, 0.65	-0.47	-1.14, 0.21	-0.16	-0.37, 0.05

* Adj 1, adjusted for age, sex, and educational level
** **p<0.05; all other comparisons NS**

Correlation

Author, Year: Tripathi, 2001	**Ref ID**: 733	**Vitamins**: B12
Objective: Review of B12 status in dementia		

Study characteristics		**Population**	**Controls***	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age: 61.6+/-6.6	60.2+/-6.6	Cases: Seen in cognitive disorders clinic, documented cobalamin level (Prospective n=54, Retrospective n=56)	Cases:	AD:	DSM-IV, NINCDS-ADRDA
	Comparative	%Male:					
	Pro/Retrospective	Race:				PD:	
Country:	India	Other:		Controls:	Controls:	Vascular dementia:	NINCDS-ARIEN
Setting:	Clinic					Other:	
Funding:	nd						
Comments:							

* Vascular or other dementias

Predictor(s): (eg, B vit level)	Outcome(s): Definition:		**Total**	**Population of interest**	**Control****
Serum B12* pg/mL	Diagnosis of AD	N enrolled:		38	62
		N analyzed:		38	62
		Drop-outs (%):			
Comments:					

* Micropore enzyme immunoassay (MPEIA). Normal: 187-1057 pg/mL; Indeterminate: 157-187 pg/mL; Low: <157 pg/mL.
** Vascular or other dementias

Other predictors/outcomes reported:			
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Mixture of prospective and retrospective		
Quality (A/B/C):	C	Applicability (1/2/3):	2

Outcome(s):	Results (Text)

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Serum B12 Low*		p	Serum B12 pg/mL		p		
		n	%		Mean	SD			
AD (probably/possible)	38	15	39.5%	<0.05	263	168	<0.05		
Vascular and other dementias*	62	8	12.9%		289	139			

* <187 pg/mL, implied
** Including mixed, diffuse Lewy body disease, infections, nutritional, head injury, systemic, extra-pyramidal, etc.

Correlation

Author, Year: Wahlin, 1996	**Ref ID**: 3433	**Vitamins**: B12, folate
Objective: To examine the relationship between low B12 (<200 pmol/L) and folate (<11 nmol/L), separately and combined, and episodic memory performance in very old age		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age: 85		Cases: Nondemented elderly	Cases: Psychiatric dx; no B-12 or folate levels; on B-12 or folate, drugs interfere with folate uptake; on neuroleptics & antidepressants without a psychiatric dx	AD:
	Comparative	%Male: 18%				
	Prospective	Race: white				PD:
Country:	Sweden	Other:		Controls:	Controls:	VascDz:
Setting:	Lived in Kungsholmen district in Stockholm					Other:
Funding:	Predoctoral fellowship grants					
Comments:						

Predictor(s): (eg, B vit level)	Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Normal B-12, normal folate	Free-Recall performance	2 memory lists of 12 concrete nouns; one list presented at a rate of 2 seconds/word, and the other presented at a rate of 5 seconds/word; subjects were told to remember as many words as possible for subsequent free-recall tests	N enrolled:	250		
Low B-12 (<200 pmol/L), normal folate	Recognition test	After free-recall of each list, yes-no recognition tests were given, in which 12 target words were presented intermixed with an equal number of detractors; participants responded orally	N analyzed:	250		
Normal B-12, low folate (<11 nmol/L)			Drop-outs (%):	0		
Low B-12, low folate						
Comments:						

Other predictors/outcomes reported:			
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:			
Quality (A/B/C):	B	Applicability (1/2/3):	3

Outcome(s):	Results (Text)
	Free Recall: Normal B-12, normal folate group performed better than Low B-12, low folate group and Normal B-12, low folate (<11 nmol/L) group by ANOVA (p<.01)
	Recognition: Normal B-12, normal folate group performed better than Low B-12, low folate group and Normal B-12, low folate (<11 nmol/L) group by ANOVA (p<.01). No significant interaction effects between vitamin group and study time in the ANOVAs
	Contrasting results from the analyses in which vitamin status was used as a categorical variable and those in which it was used as a continuous variable suggest that vitamin B12 and folate may affect episodic memory functioning only among those individuals whose vitamin levels are relatively low.

Correlation

Author, Year: Wang, 2001	**Ref ID**: 3445	**Vitamins**: B12, folate
Objective: To explore whether low serum levels of vitamin B12 and folate constitute risk factors for dementia, in particular for AD		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	Longitudinal	Age: 75-79 80-84 85-89 90-101	 n=81 n=97 n=119 n=73		Cases:	Cases:	AD:	Clinical onset and DSM III
	Non-comparative	%Male:	19%		All non demented and those without a vitamin treatment and participated in the Kungsholmen project (a large longitudinal population based study) on aging and dementia that included all inhabitants born in 1912 or earlier and lived in one area of Stockholm on October 1987.	Those who were demented and taking B 12 or folate supplementation and vascular dementia		
	Prospective	Race:	Probably 100% white				PD:	
Country:	Sweden	Other:Education >7 yr	36%		Controls:	Controls:	VascDz:	Clinical and Hachinski's scale
Setting:	Academic hospital	Alcohol consumption	78% yes		None		Other:	
Funding:	Private foundations; partly gov							
Comments:								

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
Vitamin B12	pmol/L			N enrolled:	370		
Folate	nmol/L			N analyzed:			
				Drop-outs (%):			
Comments:	2 different cutoffs were used to define folate and B12 deficiency. For B12 the lower and higher cut-off points were 151-252 pmol/L were used; and for folate it was ≤10 and ≤12 nmol/L was chosen						

Other predictors/outcomes reported:			
Follow-up duration (if applicable):	3 years		
Reasons for drop out (if applicable):			
Limitations:	2 different cut-offs		
Quality (A/B/C):	B	Applicability (1/2/3):	3

Outcome(s):	Results (Text)

Prevalence of B12 and folate deficiency at baseline (cross-sectional studies) At baseline

Description of (Sub-) Groups	N	Sr B12 ≤150 pmol/L n=58			p	Sr B12 ≤250 pmol/L n=175			p	Sr Folate n=54 ≤10 nmol/L			P	Sr Folate n=105 ≤12 nmol/L			p
		Mean	SE/SD	Prevalence		Mean	SE/SD	Prevalence		Mean	SE/SD	Prevalence		Mean	SE/SD	Prevalence	
MMSE score ≤ 26	173	nd		17.3%	NS	nd		52.6%	NS	nd		22.1%	<0.01	nd		35.5%	<0.01
MMSE score > 26	197	nd		14.2%		nd		42.6%		nd		8.2%		nd		22.4%	

Number of incident cases(n) and relative risks (RR) of Alzheimer's disease and dementia in relation to baseline vitamin levels

Description of (Sub-) Groups	N	Alzheimer's disease				N	Dementia			
		Crude RR (95% CI)		RR (Adj 1*) (95% CI)			Crude RR (95% CI)		RR (Adj 1*) (95% CI)	
B12 ≤150 vs >150 pmol/L	14 vs 46	1.7	(0.9-3.1)	1.6	(0.9-2.8)	15 vs 63	1.4	(0.8-2.4)	1.3	(0.7-2.3)
Folate ≤10 vs >10 nmol/L	12 vs	1.8	(1.0-3.4)	1.7	(0.9-3.2)	15 vs	1.7	(1.0-3.0)	1.6	(0.9-2.9)

	47					62			
B12 ≤150 or folate ≤10 nmol/L vs normal levels of both B12 and folate	26 vs 34	2.3	(1.4-3.8)	2.1	(1.2-3.5)	30 vs 48	1.9	(1.2-3.0)	1.8	(1.1-2.8)

Adj 1, adjusted for age sex and education…

AD association with 2 levels of vitamin B12 or folate

Description of (Sub-) Groups	**N**	**Alzheimer's disease**			
		RR (Adj 1*)		**RR (Adj 2*)**	
(Reference gp) Normal levels of both vitamins	34/268	1		1	
Low B12 and normal folate levels	13/47	0.7	(0.1-5.4)	0.6	(0.1-4.4)
Low folate and normal B12 levels	11/43	2.1	(1.1-4.1)	1.7	(0.9-3.3)
Low levels of both vitamins	1/11	2.3	(1.2-4.6)	1.2	(0.5-2.5)
(Reference gp) Normal levels of both vitamins	34/268	1		1	
Low levels of vit B12 or folate	25/101	2.1	(1.2-3.5)	1.4	(0.8-2.4)

Adj 1, adjusted for age sex and education…
Adj 2, adjusted for age, sex, education and cognitive functioning…

Association of vitamin levels vs normal levels stratified by cognitive functioning

Description of (Sub-) Groups	**N**	**Alzheimer's disease** Those with MMSE score ≤26			
		OR (Adj 1*)		**OR (Adj 2*)**	
(Reference gp) Normal levels of both vitamins	25/112	1		1	
Low B12 or folate levels	18/60	1.5	(0.8-2.7)		
		Alzheimer's disease Those with MMSE score >26			

(Reference gp) Normal levels of both vitamins	9/156	1		1
Low B12 or folate levels	7/41	3.1	(1.1-8.4)	

Correlation

Author, Year: Whyte, 2002	**Ref ID**: 3509	**Vitamins**: B12
Objective: To examine the relationship between B12 serum levels and cognitive and neuropsychiatric symptoms in dementia		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	78.9±7.73	75.1±7.84	Cases:	Cases:	AD:643	NINCDS-ADRDA criteria
	Comparative	%Male:	30	32	Community dwelling elderly patients who consecutively evaluated in a University Clinic between Sep 1991 and June 1999 and were found to have probable or possible AD; Low B12 ≤ 200pg/mL	ND		
	Prospective	Race:	White 97%	White 90%			PD:	
Country:	US	Education, yr	12.9±3.88	11.9±3.03	Controls:	Controls:	VascDz:	
Setting:	University Clinic (outpatients)				Community dwelling elderly patients who consecutively evaluated in a University Clinic between Sep 1991 and June 1999 and were found to have probable or possible AD; Normal B12 ≥ 201pg/mL	ND	Other:	
Funding:	ND							
Comments:	Mean age was significantly different between the 2 groups (p=0,01)							

Predictor(s): (eg, B vit level)		Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
B12	Low ≤ 200 pg/mL	Folstein MMSE, Mattis DRS, CDR scale, CERAD BRSD, Hachinski scale, Modified Rey Figure Copy, Immediate, and Delayed Recall, Verbal Fluency, Benton Visual Form Discrimination, world List Learning with Immediate and Delayed Recall	N enrolled:	643	37	606
			N analyzed:	643	37	606
			Drop-outs (%):	N/A	N/A	N/A
Comments:	ND on the methods B12 was measured; descriptions of tests are given by REF (18-24, 27-30)					

Other predictors/outcomes reported:	Regression techniques for comparing scores between different groups were adjusted for the effects of age and education

Follow-up duration (if applicable):	N/A		
Reasons for drop out (if applicable):	N/A		
Limitations:	Majority of subjects are white women; power calculations not reported		
Quality (A/B/C):	B	Applicability (1/2/3):	3

Outcome(s):	Results				
	B12 low 2 ≤ 200pg/mL	**SD**	**B12 normal ≥ 201pg/mL**	**SD**	**p**
Folstein MMSE	14.73	7.33	16.94	5.66	0.01
Mattis DRS	105.4	25.02	110.82	18.03	NS
Blessed	2.63	5.07	2.27	3.88	0.02
CDR scale (0)	1	2.7	2	0.3	NS
CDR scale (1)	18	48.7	385	63.7	NS
CDR scale (2)	13	35.1	183	30.3	NS
CDR scale (3)	5	13.5	34	5.6	NS
CERAD BRSD (total)	93.1	68.4	87.74	61.32	NS
Hachinski scale	2.97	1.72			NS
Modified Rey Figure Copy	17.46	5.61	16.03	6.64	NS
Modified Rey Immediate Recall	1.77	2.93	1.48	4.09	NS
Modified Rey Delayed Recall (0)	11	44	212	42	NS
Modified Rey Delayed Recall (<10)	15	56	225	50.5	NS
Modified Rey Delayed Recall (>10)	0	0	38	7.5	NS
Verbal Fluency	8.32	3.06	9.36	4.14	NS
Benton Visual Form Discrimination	23.59	4.74			NS
World List Learning with Immediate	3.04	1.51	2.88	2.01	NS
World List Learning with Delayed Recall	1.36	1.68	0.99	1.71	NS

Correlation

Author, Year: Woitalla, 2004	**Ref ID**: 3543	**Vitamins**: B6, B12 and folate
Objective: To compare levels of B6, B12, folate and total plasma homocysteine (t-hcys) in plasma of levodopa treated PD pts, subdivided by their MTHFR C677T genotypes and controls		

Study characteristics		**Population**	**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age: 65	58 (n=44)	Cases:	Cases:	AD:
	Comparative	%Male: 57%	51% (n=41)	PD pts only, on levodopa and dopa decarboxylas inhibitors	Metabolic disturbances like diabetes, abnormal vitamin values or vitamin supplementation	
	Prospective	Race:				PD:
Country:	Germany	Other:		Controls:	Controls:	VascDz:
Setting:						Other:
Funding:						
Comments:						

Predictor(s): (eg, B vit level)	Outcome(s): Definition:		**Total**	**Population of interest**	**Control**
PD	t-hcys	N enrolled:	127	83	44
PD with CT allele subgroup	B6	N analyzed:			
PD with TT allele subgruop	B12	Drop-outs (%):			
PD with CC allele subgroup	Folate				
Comments:					

Other predictors/outcomes reported:			
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Text description of results contradict results in tables 1 and 2 (?)		
Quality (A/B/C):	C	Applicability (1/2/3):	3

Outcome(s):	Results (Text)
	There were significant different t-hcys concentrations in PD pts and controls.
	Concentrations of B6 or B12 did nto differ, but folic acid was significantly higher in PD pts with CT allelele.
	There was no impact of the covariates (sex and age) on the results.

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Plasma t-hcys μmol/L			*p*	Sr B-6 mg/L			*p*	Sr B-12 mg/L			Sr Folate mg/L			*p*
		Mean	SE/SD			Mean	SE/SD	r=		Mean	SE/SD	r=	Mean	SE/SD	r=	
PD	83	17.9	9.84			18.7	6.69			371.45	218.43		6.39	3.31		
CT allele	38	14	5.7	CT vs. control	0.0004	20.65	7.49			322.55	119.89		7.53	3.95		
TT allele	12	22	8.58	TT vs. control	0.03	18.25	5.72			369.58	172.5		5.54	2.79		
CC allele	33	20.9	12.3	CC vs. CT	0.0029	16.62	5.43			428.42	298.7		5.39	2.14		
Control	44	13.01	5.49			19.23	8.71			417.86	232.95		6.48	2.86		

Correlation / FFQ

Author, Year: Chen, 2004	**Ref ID**: 575	**Vitamins**: Folate, B6, B12
Objective: To investigate whether intake of folate or of related B vitamins that are involved in folate and homocysteine metabolism was associated with Parkinson's disease (PD) risk		

Study characteristics		**Health Professionals Follow-up Study**		**Nurses' Health Study**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	Longitudinal	Age:	40-75	30-55	Cases: All newly developed PD cases in both Health Professional Follow-up cohort (men) and Nurse's Health cohort (women) from 1986 and from 1980, respectively, to the end of the follow-up (January 31, 2000, in men and May 31, 1998, in women)	Participants who reported PD (n=178), stroke (n=505), or cancer (other than nonmelanoma skin cancer, n=5572), at baseline were excluded from the analyses. In addition, participants with extreme daily energy intakes (<800 or >4200 kcal for men; <500 or >3500 for women) or incomplete FFQ at baseline (>70 blanks for men or >10 for women) were excluded from the analyses.	AD:	ND
	Comparative	%Male:	100	0				
	Prospective	Race:	ND	ND			PD:	After obtaining permission from participants who reported a new diagnosis of PD, a diagnosis of PD was considered definite or probable by the treating neurologist or internist, or if medical record included either a final diagnosis of PD made by a neurologist or evidence at a neurologic examination of at least 2 of the 3 cardinal signs (rest tremor, rigidity, bradykinesia) in the absence of features suggesting other diagnosis.
Country:	US	Other:			Controls: All subjects without a diagnosis of PD in the cohorts.		VascDz:	ND
Setting:	Population-based (2 large cohorts in US)						Other:	
Funding:	NIH							
Comments:	2 nested case-control studies were analyzed separately and then pooled analyses were also performed.							

		Outcome(s):	Definition:		Total	Population of interest	Control
				N enrolled:	136,057	N/A	N/A
Folate intake quintiles	FFQ during the previous 12 months, with 9 possible response categories ranging from "never" to "6 or more times per day." Information on the dose and duration of supplemental use of specific vitamins and multivitamins was also collected. The nutrient composition of foods was estimated from the Harvard University Food Composition Database that was derived from the US Department of Agriculture and supplemented with information from manufacturers and data from peer-reviewed literature. Validations studies have been done.	RR of PD	Cox proportional hazard models controlling for age, smoking status, caffeine intake, alcohol consumption, and lactose intake.	N analyzed:	136,057	415	135,642
Vitamin B6 intake quintiles				Drop-outs (%):	N/A		
Vitamin B12 intake quintiles				Note: Original cohort was51,529+121,700. 21% participants were not included in the analyses due to various reasons stated in the exclusion criteria.			
Folate supplement use	Nonusers, < 400 µg/day, ≥ 400 µg/day	Pooled RR of PD	Log relative risks (RRs) from the 2 cohorts were pooled by the inverse of their variance.				
Vitamin B6 supplement use	Nonusers, < 1.7 mg/day, ≥ 1.7 mg/day						
Vitamin B12 supplement use	Nonusers, < 2.4 µg/day, ≥ 2.4 µg/day						
Comments:	The p value for linear trend was calculated by using the median of each quintile category as a continuous variable in the Cox models.						

Other predictors/outcomes reported:			
Follow-up duration (if applicable):	An average of 12.7 years in men and 17.3 years in women		
Reasons for drop out (if applicable):			
Limitations:			
Quality (A/B/C):	A	Applicability (1/2/3):	3

Outcome(s):	Results (Text)
RR of PD	Controlling for age, smoking, alcohol consumption, caffeine intake and lactose intake, there was no significant associations found between the baseline intake of folate, vitamin B6, or vitamin B12 in the Health Professionals Follow-up study (1986-2000) and the Nurse's Health Study (1980-1998) and multivariate relative risk of Parkinson's disease: all RRs in each quintile were not statistically different from 1.0 and the p values for the trend of RRs across quintiles for all vitamin examined were not significant. Individuals at either the low end (≤200 μg/day) or the high end (>1000 μg/day) of folate intake had a Parkinson's disease risk similar to the risk of those with normal folate intake, controlling for age, smoking, alcohol consumption, caffeine intake and lactose intake. Supplemental intake of folate, vitamin B6, or vitamin B12 was also not related to the risk of Parkinson's diseases. Compared with nonusers, individuals whose supplemental folate intake was more than 400 μg/day had a pooled RR of 1.0 (95%CI: 0.8, 1.2)

Note: Detail RR data by quintiles or by supplemental intake categories were showed in tables.

Correlation / FFQ

Author, Year: Deijen, 2003	**Ref ID**: 765	**Vitamins**: B1, B2, B6
Objective: To elucidate the relation between nutritional intake and daily functioning in psycho-geriatric elderly people		

Study characteristics		**Population**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS & Longitudinal	Age: 83.0±7.0 SD	110 psycho-geriatric residents of a nursing home	Psychiatric history, need of terminal care, suffering from cancer, rheumatoid arthritis, insulin dependent diabetes, serious overweight (BMI > 30 kg/m2), having a fiber-poor diet or a diet that can not be combined with food supplementation; younger than 65 years. The data from 20 subjects were excluded from evaluation due to incomplete data or failure to complete the total investigation period.	AD: ND
	Non-Comparative	%Male: 13% (12/90)			
	Prospective	Race: ND			PD: ND
Country:	Netherlands	BMI: 24.9±4.0			VascDz: ND
Setting:	Nursing home				Other:
Funding:	Numico Research B.V.				
Comments:	During the study 60% of the dropouts became ill against 34% of the subjects who completed the study. In addition, within the group of dropouts, the percentage of males was higher than that of the study group (30% and 13% respectively)				

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**
				N enrolled:	110	110
Thiamin intake (?)	A combination of a 3-day record and weighing-back methods at baseline, week 8, 16 and 24 (Nurses recorded).	Zorg Index Geriatrie (ZIG)-scales	The ZIG-scale consists of the ZIG-A scale (cognitive functioning), ZIG-B scale (physical functioning) and the ZIG-C scale (social functioning). The ranges of the ZIG-scales are from 6 to 24. The nursing-home caregiver(s) assessed subject's ZIG-scales.	N analyzed:	90	90
Riboflavin intake (?)				Drop-outs (%):	18%	18%
Vitamin B6 intake (mg)						
Comments:	For the purpose of this review, only ZIG-A scale (cognitive functioning) is the outcome of interest. In correlation analyses, nutrition parameters were averaged for each subject across the 12 assessments: 3 across 1 week, 4 across 24 weeks. To determine possible relationships between the various nutrient s and ZIG-scores, partial correlations, controlling for BMI were computed. All bivariate correlations were computed by two-tailed tests. In longitudinal analyses, repeated measures analyses on the 4 data point (week 0, 8, 16 and 24) of the ZIG-scores and nutrient intakes were used.					

Other predictors/outcomes reported:	Age; weight; BMI; energy, vitamin A, niacin, vitamin C intakes
Follow-up duration (if applicable):	6 months
Reasons for drop out (if applicable):	Incomplete data or failure to complete the total investigation period. During the study 60% of the dropouts became ill against 34% of the subjects who completed the study.
Limitations:	Subjects were recruited from a nursing home (limited applicability). Dropouts had worse health status than the completers. If the outcome assessors (nursing-home caregivers) and the exposure assessors (nurses) were the same, a dependent misclassification bias would occur. The results clearly showed that subjects with high vitamin and energy intake were younger than those with a lower intake. However, the correlation analyses only controlled for BMI not age.
Quality (A/B/C): C	Applicability (1/2/3): 2

Outcome(s):	Results (Text)
ZIG-A (cognitive) scale	Longitudinal analysis (repeated measurements analyses) were carried out with ZIG-scores as repeated measurement factor and 3 comparisons were separately made between low/high intake groups of vitamin B-6 as between subjects factor. The 2 experimental groups were formed based on high and low intakes of nutrients compared to the median intakes at baseline. There were no interactions between intake groups and week, indicating that the high and low intake groups had the same pattern of ZIG-scores across the 6-month experimental period. Disregarding the factor intake group, a significant increase in all ZIG scales was found across weeks ($p<0.0005$) indicating that a deterioration in cognitive, physical and social functioning takes place in the course of the 6-month study period. No significant increase of dietary vitamin B6 was seen across weeks.

Correlation of Predictors with Outcomes (cross-sectional studies)

Outcome	N	Mean intake of Thiamin (unclear unit)		Mean intake of Riboflavin (unclear unit)		Mean intake of Pyridoxine (unclear unit)	
		r=*	*p*	r=*	*p*	r=*	*p*
ZIG-A (cognitive) scale, higher scores indicate worse cognitive function	90	0.25	0.02	0.23	0.03	ND	NS

*Partial correlations, controlling for BMI

Correlation / FFQ

Author, Year: Lee, 2000	**Ref ID**: 1813	**Vitamins**: B1; B2
Objective: To analyze the association between dietary intake and cognitive function of the Korean elderly		

Study characteristics		**Population**	**Men**	**Women**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	72.3±6.5 SD	69.6±6.0	A random sample of elderly people who usually spend the daytime at the welfare center	Major cognitive function impairment.	AD:	ND
	Non-Comparative	%Male:	47% (210/449)					
	Prospective	Race:	Koran				PD:	ND
Country:	Korea	BMI:	23.3±3.4	24.5±4.1*			VascDz:	ND
Setting:	Community (primarily 2 elderly welfare centers)	WHR:	0.91±0.05	0.88±0.05*			Cognitive function was classified according to MMSE-K scores: normal (≥24), inadequate (19-24), and poor (≤19)	
			*p<0.01 b/w groups					
Funding:	University							
Comments:	Due to many significant differences in the anthropmetric measurements (e.g. BMI, height, weight, waist/hip ratio (WHR)), results for men and women should be discussed separately because all analyses were univariate. MMSE-K (Mini-Mental State Examination for Koreans) modified from Folstein et al's MMSE.							

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**	**Control**
				N enrolled:	449	449	
Thiamin intake (mg)	Single 24-hr recall	MMSE-K Status	Points ranged from 0 to 30. Normal (≥24), inadequate (19-24), and poor (≤19)	N analyzed:	449	449	
Riboflavin intake (mg)	Single 24-hr recall			Drop-outs (%):	N/A		
Comments:	24 h diet recalls were done by a trained interviewer and with the use of food models. Nutrient intakes were calculated using the Computer Aided Nutritional (CAN) analysis software program developed by The Korean Nutrition Society. Incomplete and inconsistent data were excluded.						

Other predictors/outcomes reported:	Age; education level; BMI; WHR; Food intakes; intakes of the major macro- and micro- nutrients		
Follow-up duration			
Reasons for drop out			
Limitations:	Single 24-hr dietary recall cannot account for the day-to-day variations of nutrient/food intakes. Subjects may not represent the general elderly population in Korea. Age and education levels were found to be strongly related to cognitive function in both men and women, but most analyses of the association between food/nutrient intakes and MMSE-K status were not adjusted for these confounders. Elderly with higher education levels or younger age could give a more accurate 24-hr dietary recall, resulting in biases away from the null.		
Quality (A/B/C):	C	Applicability (1/2/3):	2

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N	Dietary Intake of Thiamin (mg)			*p*	Dietary Intake of Riboflavin (mg)			*p*
		Mean	SD	r=**		Mean	SD	r=**	
Men –									
Normal (≥24)	136	0.95	0.35			0.87	0.46		
Inadequate (19-24)	48	0.91	0.34	0.083	NS	0.77	0.37	0.082	NS
Poor (≤19)	26	0.82	0.27			0.74	0.32		
Women –									
Normal (≥24)	86	0.91	0.39			0.68	0.33		
Inadequate (19-24)	79	0.90	0.63	0.125	NS	0.72	0.50	0.144	<0.05
Poor (≤19)	74	0.71*	0.35			0.50*	0.32		

*values are significantly lower, $p<0.05$ by Duncan's multiple range test
**age controlled

Correlation / FFQ

Author, Year: Mizrahi, 2003	**Ref ID**: 2188	**Vitamins**: B6; folate
Objective: To examine the relationships of total plasma homocysteine levels (tHcy), dietary vitamin B6 and folate, ApoE genotype, cognitive performance, blood lipids and serum albumin in Alzheimer's disease (AD) patients and healthy controls		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	Case-Control study	Age:	74.1±7.9 SD	74.6±6.9	Cases:	For all participants:	AD:	Diagnosis of probable AD, fulfilling NINCDS/ADRDA criteria
	Comparative	%Male:	45.3	45.3	Cases were recruited from a Research Registry at an Alzheimer Center. Cases were matched by gender, year of birth, and smoking status to a pool of 382 healthy controls using propensity scores.	Presence of pernicious anemia, renal impairment, hypothyroidism, carcinoma of the breast, ovary and pancreas, severe psoriasis, and drugs (folate antagonists: methotrexate, phenytoin and carbamazepine and B6 antagonists: theophylline, azarabine, oestrogen-containing oral medications) known to increase tHcy levels	PD:	ND
	Retrospective	Race:	ND	ND			VascDz:	ND
Country:	US	%Current smokers:	4.7	6.3	Controls:		Other:	
Setting:	Registry	Education, years	12.5±2.9	15.2±2.8*	Controls age 60 years or older were recruited from friends or neighbors of cases or members of the organizations to which cases belonged.			
		MMSE score (maximum 30)	17.7±6.8	28.8±1.1*				
		%ApoE genotype, with 1 or 2 epsilon 4	61.7	14.3*				
		*p<=0.001 between groups						
Funding:	Non-profit organizations; NIH							
Comments:	Matched pairs analysis was only performed for the relationship between tHcy levels and the odds ratio for AD, which was not directly of interest to our report. The relationships between B6 or folate intakes and AD were done using unmatched analysis (two-sample t-tests), which doses not adjust for the necessary covariates.							

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		Total	Population of interest	Control
				N enrolled:	446	64	382
Vit. B6 intake (mg/1000Kcal)	FFQ adapted from the Block Health Habits and History Questionnaire (HHHQ). Medium-sized portion is assumed for every food. Nutrient analyses of dietary consumption used folate values in foods before the US FDA made folate enrichment mandatory in January 1998.	AD patients vs. healthy controls	Two-sample t-tests for detecting differences between the 2 groups at 3 age periods: 20-39 years, 40-59 years, and 60+. Spearman correlation was used for correlations between tHcy levels and dietary Vit B6 and folate being consumed in the 3 age periods between AD patients or controls separately.	N analyzed:	128	64	64
Folate intake (mg/1000Kcal)				Drop-outs (%):	N/A	Control dropouts were due to matching	83%
tHcy (µmol/L)	Samples were run on the Abbot Imx Platform, which is a fluorescence polarization immunoassay						
Comments:	Missing data on dietary intake for some of the participates resulted in slightly different sample sizes for the various time periods.						

Other predictors/outcomes reported:	ApoE genotype; triglycerides; cholesterol; LDL
Follow-up duration	
Reasons for drop out	
Limitations:	FFQ is subject to recall biases and not a good method to assess absolute amount of dietary intakes. Controls might have more accurate recalls than the cases, because proxy or surrogate respondents were used to estimate cases' intake during 3 age periods (20-39 years, 40-59 years, and 60+ years)! Two-sample t-tests were used to compare the mean levels of dietary folate and vitamin B6 for AD patients and controls at 3 age periods: 20-39 years, 40-59 years, and 60+. This analysis dosen't adjust for the necessary covariates.
Quality (A/B/C): C | Applicability (1/2/3):	3

Outcome(s):	Results (Text)
AD patients vs. healthy controls	No statistically significant correlations were found between tHcy levels and dietary vitamin B6 and folate being consumed in the 3 age periods between AD patients or controls (Spearman correlation; $p>0.05$) AD patients had lower mean dietary vitamin B6 intake than controls in the 60+ years age period ($p=0.05$), but no differences in their 20-39 years ($p=0.58$) and 40-59 years age periods ($p=0.61$). AD patients had lower mean dietary folate intake than controls in the 60+ years age period ($p=0.01$), but no differences in their 20-39 years ($p=0.6$) and 40-59 years age periods ($p=0.14$). Note: Data for the dietary B6 and folate intakes were reported in figures.

Correlation / FFQ

Author, Year: Renvall, 1989	**Ref ID**: 2686	**Vitamins**: B1, B2, Folate, B12
Objective: To test the hypotheses that dietary intake and biochemical values of vitamin B12, folate, thiamine and energy would be lower in senile dementia of the Alzheimer's type (SDAT) patients than in elderly patients with normal cognition.		

Study characteristics		**Population** ♂	♀	**Controls** ♂	♀	**Inclusion criteria**	**Exclusion criteria**	**Definitions**	
Study design	XS	Age:	75.4	77.9	71.1	71.4	Cases:	For all participants:	AD:	ND
	Comparative	%Male:	32%(7/22)		38%(13/41)		Program participants who had a diagnosis of senile dementia of the Alzheimer's type (SDAT)	Subjects who did not complete the 3-day dietary record (n=6).	PD:	ND
	Prospective	Race:	ND		ND			Not all biochemical values were obtained from the subjects completing the dietary record. Information for each parameter is presented only for those subjects from whom both dietary and biochemical data were available.		
Country:	US	%Multi-Vit users:	50%	48%	53%	42%	Controls: Elderly people (program participants) who were at least 60 years of age and free from acute illness or recent hospitalization.		VascDz:	ND
Setting:	Outpatient geriatric assessment program								SDAT:	Diagnosis was determined by consensus of the medical team composed of internists, psychiatrists, and neurologists
Funding:	NIH									
Comments:	There was also a retrospective study (serum vitamin status only). Only the prospective study is reviewed here. SDAT patients (or population of interest) were significantly older than normal subjects. Biochemical values, age, MMSE scores and living situation did not differ between the excluded and included subjects. Mean body weight of the excluded subjects was significantly ($p<0.006$) lower than that of the participants.									

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		Total	Population of interest	Control
				N enrolled:	69	ND	ND
Thiamin intake (mg/day) (n=48)	Subjects or their caregivers were given oral and written instructions in keeping written 3-day food consumption records. The records were analyzed by computer program (Ohio State University) and missing values were added from atandard handbooks of food composition. Multivitamin supplements were taken sporadically by many of the subjects; therefore, values from supplements were not added to those of the diets.	SDAT vs. normal subjects	ANOVAR followed by Bonferroni tests, when appropriate, was used to measure differences among means for dietary and biochemical parameters. For this analysis, subjects were grouped by 1) cognition; 2) sex and cognition; or 3) supplement use and cognition	N analyzed:	<63	<22	<41
Riboflavin intake (mg/day) (n=51)				Drop-outs (%):	>8.7%		
Folate intake (µg/day) (n=37)							
Vitamin B12 intake (µg/day) (n=43)							
Blood thiamin level	Activity of RBC transketolase assay						
Riboflavin ratio	The riboflavin content of casual urine samples was measured fluorometrically and corrected by creatinine concentration.						
Comments:	Dropout rates were larger than 8.7% because only subjects who had both dietary and biochemical data were analyzed.						

Other predictors/outcomes reported:	Protein, energy, and iron intakes; RBC folate and serum vitamin B12; serum protein; serum albumin; hematocrit; hemoglobin		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Only subjects who had both dietary and biochemical data were analyzed. Dropout rate for some measures were as high as 41%. 3-day dietary records by subjects or their caregivers. No description which days in a week. The self-reported dietary intake and the biochemical values (blood markers) were weekly correlated. Correlation coefficients (data not shown) between the measures of nutritional status were higher in normal subjects than in SDAT subject. This indicates SDAT subjects had poorer dietary recalls. This confounding factor was not adjusted for in the analyses.		
Quality (A/B/C):	C	Applicability (1/2/3):	2

Correlation of Predictors with Outcomes (cross-sectional studies)

	SDAT subjects	Normal Subjects
Dietary values	**Mean±SD [95%CI]**	**Mean±SD [95%CI]**
Thiamin, mg/day (n=48, p<0.54)	1.4±0.8 (n=15) [0.9-1.8]	1.2±0.4 (n=33) [1.1-1.4]
Riboflavin, mg/day (n=51, p<0.66)	1.6±0.6 (n=14) [1.3-1.9]	1.5±0.6 (n=37) [1.3-1.7]
Folate, µg/day (n=37, p<0.54)	169±74 (n=27?) [140-198]	186±71 (n=10) [135-236]
Vitamin B12, µg/day (n=43, p<0.31)	2.3±1.8 (n=21?) [1.5-3.1	2.9±2.3(n=22) [2.0-4.0]
Biochemical values	**Mean±SD [95%CI]**	**Mean±SD [95%CI]**
Thiamin		
ETKAS, IU/ml/hr (n=48, p<0.49)	4.3±1.6 (n=15) [3.4-5.2]	3.9±1.6 (n=33) [3.3-4.5]
ETKAPH, IU/min/g hemoglobin (n=51, p<0.055)	1.5±0.5 (n=14) [1.3-1.8]	1.89±0.4 (n=28) [1.7-2.0]
Riboflavin ratio (n=51, p<0.44)	1.9±1.9 (n=14) [0.8-3.0]	3.1±5.9 (n=37) [1.1-5.1]

? Questionable values perhaps due to reporting errors

	Supplement Users		Supplement Nonusers	
	SDAT	Normal	SDAT	Normal
Biochemical values	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**
Thiamin				
ETKAS, IU/ml/hr (n=48, p<0.48)	4.6±2.0 (n=7)	3.8±1.7 (n=18)	3.9±1.2 (n=8)	4.0±1.5 (n=15)
ETKAPH, IU/min/g hemoglobin (n=51, p<0.03)	1.7±0.3 (n=6)	1.9±0.4* (n=15)	1.4±0.6* (n=8)	1.7±0.3 (n=13)
Riboflavin ratio (n=51, p<0.01)	2.7±2.1 (n=8)	4.7±7.6 (n=21)	0.8±0.6 (n=6)	1.0±0.6 (n=16)

* Significantly different means by Bonferroni correction: p<0.01

Correlation / FFQ

Author, Year: Requejo, 2003	**Ref ID**: 2687	**Vitamins**: B1, B2, B6, Folate; B12
Objective: To study the importance of nutrition in the maintenance of cognitive function in a group of elderly people.		

Study characteristics		**Population**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	XS	Age: ≥ 65	Noninstitutionalized elderly people (≥ 65 y) who spent part of their time at day centers	Any disease that might affect the food intake (neoplasms, liver or kidney disease, diabetes, etc), took medications that might influence the appetite, trying to gain or lose weight; manifest cognitive decline (MMSE<24)	AD: ND
	Non-Comparative	%Male: ND			
	Prospective	Race: ND			PD: ND
Country:	Spain	Other:			VascDz: ND
Setting:	Community				Other:
Funding:	ND				
Comments:					

Predictor(s): (eg, B vit level)		Outcome(s):	Definition:		**Total**	**Population of interest**
				N enrolled:	168	168
Thiamin intake (mg/day)	Precise individual weighing of food was performed for 5 days in order to monitor the food consumed at the midday meal, the only meal the subjects took at the centers. A 7-day food record was also kept, in which subjects noted all the foods they consumed. The energy and nutrient contents of the foods and drinks consumed were determined using the Institution of Nutrition's Food Composition Tables (Instituto de Nutricion, 1994)	Cognitive capacity	Folstein's MMSE was used. Points are awarded between 0 and 35, with 28 or more considered as normal.	N analyzed:	168	168
Riboflavin intake (mg/day)				Drop-outs (%):	N/A	
Pyridoxine intake (mg/day)						
Folate intake (µg/day)						
Vitamin B12 (µg/day)						
Comments:	Since the test results get worse with advancing age (r=-0.2730, p<0.001), subjects were also grouped with respect to this parameter (either above or below the 75th percentile (74.8 y]). The chi-square test was used to confirm the homogeneity of gender distribution between these groups.					

Other predictors/outcomes reported:	Age; food consumption; other major macro- and micro- nutrients		
Follow-up duration (if applicable):			
Reasons for drop out (if applicable):			
Limitations:	Subjects may not represent general elderly people in Spain		
Quality (A/B/C):	B	Applicability (1/2/3):	2

Correlation of Predictors with Outcomes (cross-sectional studies)

Description of (Sub-) Groups	N=168	Dietary Intake of Thiamin (mg/day) Mean	SD	p	Dietary Intake of Riboflavin (mg/day) Mean	SD	p
MMSE ≥ 28							
Age < 75th percentile	ND	1.12 [a]	0.34		1.43 [a]	0.40	<0.05**
Age ≥ 75th percentile	ND	1.12 [a]	0.44	<0.1*	1.52 [b]	0.43	
MMSE < 28							
Age < 75th percentile	ND	1.05 [b]	0.29		1.39 [a]	0.35	<0.05**
Age ≥ 75th percentile	ND	0.96 [b]	0.23		1.46 [b]	0.38	

Difference in the subscripts indicates statistical significant differences between the groups.
*Differences obtained with respect to MMSE score
** Differences obtained with respect to age

Description of (Sub-) Groups	N=168	Dietary Intake of Pyridoxine (mg/day) Mean	SD	p	Dietary Intake of Folates (µg /day) Mean	SD	p
MMSE ≥ 28							
Age < 75th percentile	ND	1.40	0.39	NS	202.0 [a]	73.7	
Age ≥ 75th percentile	ND	1.36	0.48		222.9 [a]	113.8	
MMSE < 28							<0.05*
Age < 75th percentile	ND	1.39	0.32	NS	182.9 [b]	60.5	
Age ≥ 75th percentile	ND	1.40	0.31		180.5 [b]	64.3	

Difference in the subscripts indicates statistical significant differences between the groups.
*Differences obtained with respect to MMSE score

Description of (Sub-) Groups	N=168	Dietary Intake of Vitamin B12 (µg /day)		*p*
		Mean	SD	
MMSE ≥ 28				
Age < 75th percentile	ND	7.3	7.9	NS
Age ≥ 75th percentile	ND	7.3	5.4	
MMSE < 28				
Age < 75th percentile	ND	5.9	5.6	NS
Age ≥ 75th percentile	ND	7.4	8.0	

Berry Evidence Tables – Animal / In Vitro Studies

Author, Year	Saija, 1990
Central hypothesis/Stated Purposes of Study	Myrtillinum (a purified Bilberry extract containing 15 anthocyanins) has capacity to affect T3 transport into brain in euthyroid rats
Hypothesis diagram	Myrtillinum administration → changes in T3 transport into brain
Experimental diets or reagents	Myrtillinum (a purified Bilberry extract containing 15 anthocyanins) was injected intraperitoneally at the dose of 200 mg/Kg/day for 3 consecutive days.
Control diets or reagents	Vehicle (26% ethanol/water, v/v; volume of injection: 0.2 ml/100 g body weight) injections
Study characteristics	Country: Italy Funding source: ND
Gap in Knowledge	Known: Flavonoids have been demonstrated to be potent non-toxic iodothyonine deiodinase inhibitors in microsomal membranes and in intact rat hepatocytes; they are specific high-affinity competitors for L-thyroxine (T4) binding to human T4-binding prealbumin, and very poor inhibitors of 3,3',5-triiodothyronine (T3) binding to the nuclear T3 receptors. Unknown: The effects of myrtillinum (a purified Bliberry extract) on T3 transport into brain
Experimental model	Brain of adult Sprague-Dawley rats (330-350 g body weight)
Study design	24-hr after the last injection, both vehicle- and myrtillinum-injected rats were decapitated 15 sec after anesthesia and the brain removed; tissue specimens were dissected from the ipsolateral hemisphere.
Final sample size	No Data
Duration	3 days
Measurements / Endpoints / Outcomes of interest	Percent brain uptake index of [^{125}I]L-T3, analyzed by different brain fractions
Other outcomes reported	
Results	Administration of myrtillinum induced a significant increase in T3 transport into frontal cortex, temporoparietal cortex, occipital cortexs, hippocampus, thalamus, hypothalamua and brain-stem ($p<0.05$). No significant change in T3 transport into striatum, inferior colliculus, and cerebellum.
Authors' Conclusions	Administration of myrtillinum induced a significant and widespread increase in T3 transport into brain.
Quality	B
Limitations / Comments	There was no expected direction of effects of myrtillinum on T3 transport into brain to begin with. The primary goal of this short study (only 2 pages) is to find out what will happen and generate some possible hypotheses. Not sure how relevant of the findings from this study to the neurodegenerative diseases. No data on the numbers of animals

Author, Year	**Wang, 1996**
Central hypothesis/Stated Purposes of Study	To show the differential inhibition of eukaryote protein kinases by condensed tannins prepared from a variety of plant sources, including gooseberry (*Ribes grossularia* fruit), red currant (*Ribes rubrum* fruit), blueberry *(Vaccinium corymbosum* fruit) … etc.
Hypothesis diagram	Condensed tannins isolated from fresh fruits → inhibit PKC activities
Experimental diets or reagents	Condensed tannins (polymers consisting of flavan monomers, such as procyanidin and prodelphinidin units) isolated from fresh fruits (inhibitors), including gooseberry (exp#6), red currant (exp#17), and blueberry (exp#18). The composition and relative stereochemistry proportions of these tannins are as below:

Tannin preparation	*cis/trans*	Procyanidin/prodelphinidin	M_N
Gooseberry tannin	63/37	77/23	2700
Red currant tannin	24/76	78/22	2700
Blueberry tannin	100/0	96/4	3500

Control diets or reagents	N/A
Study characteristics	Country: New Zealand Funding source: Australian Research Council; University fund
Gap in Knowledge	Known: Previous study showed that a range of condensed tannin deriving from the cladodes of *Phyllocadus trichomanoides*, the bark *of Pseudotsuga menziesii* and the heartwood of *Acacia melanoxylon* are potent inhibitors of PKC and CDPK while being in general relatively poorer inhibitors of cAK. Unknown:
Experimental model	Rat brain PKC (specific activity 0.6 μmol min^{-1} mg $protein^{-1}$ with 3.5 μM EGFRP as substrate) was extensively purified and assayed in standard assay conditions. Inhibitor IC_{50} values (concns for 50% inhibition of particular protein kinases in the standard assay conditions) were determined from interpolation of plots of protein kinase activity versus inhibitor concn. Control protein kinase activity (no added inhibitor) was routinely determined 6 times and assays with inhibitor included were determined in duplicate. All assay results were corrected by subtraction of blank values from assays conducted in the absence of added protein kinase.
Study design	In vitro
Final sample size	N/A
Duration	N/A
Measurements / Endpoints / Outcomes of interest	Inhibitor IC_{50} values (μM) of rat brain protein kinase C (PKC)
Other outcomes reported	The composition and relative stereochemistry proportions of condensed tannin preparations Inhibitor IC_{50} values (μM) of chicken gizzard myosin light chain kinase (MLCK), wheat embryo CDPK, and rat liver cyclic AMP-dependent protein kinase catalytic subunit (cAK)
Results	Tannin preparations from gooseberry (exp#6), red currant (exp#17), and blueberry (exp#18) have similar effectiveness as inhibitors of rat brain PKC with IC_{50} values (0.7, 0.6, and 0.5 μM respectively) as each other and compared to other plant tannins.
Authors' Conclusions	Tannin preparations from gooseberry, red currant, and blueberry have similar effectiveness as inhibitors of rat brain PKC
Quality	A
Limitations / Comments	Not sure how relevant of the findings from this study to the neurodegenerative diseases.

Author, Year	Joseph, 1998A [UI#9928436] and Bickford, 1999*
Central hypothesis/Stated Purposes of Study	Diets supplemented with vitamin E, strawberry extracts, spinach, or blueberry extracts may help animals resistant to the deleterious effects of 48 h of 100% oxygen exposure (normobaric hyperoxia) on several neuronal parameters
Hypothesis diagram	Dietary antioxidants ↓ Oxidative stress (OS) due to hyperoxia → X → reduce β -adrenergic receptor function in the cerebellum
Experimental diets or reagents	Strawberry diet: control diet supplemented with strawberry extracts (9.4 g/kg dried aqueous extract) Blueberry diet: control diet supplemented with blueberry extracts (10 g/kg dried aqueous extract)
Control diets or reagents	AIN-93
Study characteristics	Country: US Funding source: No data
Gap in Knowledge	Known: Research has indicated that animals maintained on diets containing fruits or vegetables that are high in antioxidant activity are more resistant to the deleterious effects of 48 h of 100% oxygen exposure on several neuronal parameters that also show declines in aging. Unknown: The effects of diets supplemented with vitamin E, strawberry extracts, spinach, or blueberry extracts on several neuronal parameters. [Note: for the purpose of this review, only diets supplemented with strawberry extracts, blueberry extracts, and control diet are of interest]
Experimental model	6- to 8- month-old F344 rats
Study design	Rats were fed the experiment or control diets for 8 weeks prior to 48 h of normobaric hyperoxia.
Final sample size	No data
Duration	8 weeks
Measurements / Endpoints / Outcomes of interest	Dopamine release in striatal β -adrenergic receptor function in the cerebellum: isoproterenol modulation of GABA cerebellar Purkinje neurons (% cells modulating).
Other outcomes reported	
Results	Data for the results of dopamine release in striatal is not shown. Rats fed diets supplemented with strawberry extracts were protected from the damaging effects of hyperoxia as shown in the β -adrenergic receptor function of the cerebellar purkinje neurons ($p<0.01$).
Authors' Conclusions	Diets supplemented with strawberry extracts and blueberry extracts were both effective in striatal oxotremorine enhancement of dopamine release (data not shown) and β -adrenergic receptor function in the cerebellum.
Quality	C
Limitations / Comments	Joseph, 1998A is a review article with a paragraph reporting the preliminary data. Later, the data was published in one section of results in Bickford, 1999 The amount of added food extracts at 1.36 mmol Trolox equivalents as determined by the ORAC assay. Limited data presented in the articles and need to cross reference for more complete reporting. Unclear methods.

***This is a review article with some primary data in "3.4. Effects of hyperoxia on cerebellar physiology: nutritional interventions"**

Author, Year	Joseph, 1998B [UI#9742171]
Central hypothesis/Stated Purposes of Study	Role of long term feeding dietary phytochemicals and antioxidants to ameliorate or prevent age related decline in CNS functions and neurodegenerative diseases
Hypothesis diagram	Oxidative stress may be a factor in neuronal loss in aging and enhanced loss in age-related neurodegenerative diseases; hence reduction in OS with exogenous antioxidant may help
Experimental diets or reagents	Strawberry 9.5 g/kg diet (also spinach and Vit E groups)
Control diets or reagents	Modified AIN-93 diet (described in table 1)
Study characteristics	Country: US Funding source: Government
Gap in Knowledge	Known: OS may play an etiological role in age related neurodegeneration and there is an age related decrease in the endogenous antioxidants. Diets rich in fruits and vegetables have high antioxidants Unknown: Role of exogenous antioxidants to prevent loss of Ca homeostasis and loss of cognitive performance
Experimental model	Male Fischer rats, from age 6-15 months
Study design	Randomized controlled trial
Final sample size	80 in total
Duration	8 months
Measurements / Endpoints / Outcomes of interest	DA release from striatal slices, ^{45}Ca recovery, cognitive testing, oxidative stress, GTPase activity
Other outcomes reported	Electrophysiology, weights and food intakes
Results	DA release: (assumed 8 animals per group) Significant oxotremorine-enhanced K+ evoked striatal dopamine release (K+ ERDA) from animals maintained on strawberry diet compared to control diet ($p<0.034$). ^{45}Ca recovery was significant greater in strawberry group exposed to H_2O_2 treatment but not in control diet group exposed to H_2O_2 .($p<0.02$) In the control diet ^{45}Ca recovery was significantly decreased in the H_2O_2 exposed than non exposed controls.($p<0.001$) Cognitive testing: Morris Water maze trial 1 showed a significant effect for strawberry group for latency ($p<0.05$) and distance ($p<0.01$). No difference between strawberry and control on working memory trial 2 performance Oxidative stress: In the cerebellar tissue strawberry group showed increased native protection compared to the control group ($p<0.0001$). GTPase activity: Age-induced decrements in carbachol stimulated GTPase activity were significantly less with strawberry than control ($p<0.0001$).
Authors' Conclusions	Phytochemicals present in antioxidant rich foods such as spinach may be beneficial in retarding functional and age-related CNS and cognitive behavioral deficits
Quality	A
Limitations / Comments	Pre trial data on the animals unknown

Author, Year	Bickford, 1999*
Central hypothesis/Stated Purposes of Study	If oxidative stress is important for the development of age-related declines in CNS function, then treatment of rats with antioxidants should prevent some of the neurodegenerative alterations observed during the aging process.
Hypothesis diagram	Diets supplemented with antioxidants → delay the onset of age-induced alterations in cerebellar physiology and delay motor learning declines
Experimental diets or reagents	Not reported, but presumable same as previous study, as below: Strawberry diet: control diet supplemented with strawberry extracts (9.4 g/kg dried aqueous extract) Blueberry diet: control diet supplemented with blueberry extracts (10 g/kg dried aqueous extract)
Control diets or reagents	Not reported, but presumable same as previous study: AIN-93
Study characteristics	Country: US Funding source: No data
Gap in Knowledge	Known: The noradrenergic input to cerebelaar Purkinje neurons inhibits spontaneous discharge and thus has been previously characterized as a 'modulatoray" input. It has been shown that NE, applied iontophoretically or via activation of the locus coeruleus, will potentiate GABA-induced inhibitions of cerebellar Purkinje neurons via the β-adrenergic receptor. This effect of NE is altered in aged rats such only 30% of cells in aged rats demonstrate this effect whereas 70%-80% of neurons recorded in young animals will show an increase in the response to GABA during application of isoproterenol (ISO). Depletion of cerebellar NE or blockade of β-adrenergic receptors impairs the ability of rats to improve performance on a runway task where the rats must learn to walk on varying patterns of pegs that protrude from the runway walls. Unknown:
Experimental model	6-month-old F344 rats
Study design	Rat fed diets supplemented w/ (vitamin E), strawberry extracts, (spinach), or blueberry extracts, compared to those fed control diet.
Final sample size	No data
Duration	Long-term feeding: 9 months Short-term feeding: 2 months
Measurements / Endpoints / Outcomes of interest	Long-term feeding: β -adrenergic receptor function in the cerebellum: % neurons Short-term feeding: Rod walking motor learning task: Data collection begins when rat has performed 2 successful traverses of the entire length of the uncovered rods in less than 1 min. Daily performance calculated by determining the running time for 20 successive trials/day. Sessions are conducted for 5 days during this phase of training. (This measure was done for short-term feeding study only) ISO potentiation of GABA
Other outcomes reported	
Results	Long-term feeding: Strawberry supplemented diet improved β -adrenergic receptor function in the aged rats when compared to control diet fed animals of the same age ($p<0.01$) Short-term feeding: Data not shown
Authors' Conclusions	Long-term feeding: Long-term feeding of diets high in antioxidant potential is capable of delaying the onset of age-induced alterations in cerebellar physiology. Short-term feeding: Diets supplemented with strawberry extracts and bluebecrry extracts for 2 months reversed the age-related decline in both ISO potentiation of GABA and in motor learning.
Quality	C
Limitations / Comments	Limited data presented in the articles and need to cross reference for more complete reporting; Unclear methods

***This is a review article with some primary data in "3.5. Effects of nutritional intervention on cerebellar physiology"**

Author, year	Joseph, 1999
Central hypothesis/Stated Purposes of Study	To examine whether dietary supplementation with spinach, strawberry, or blueberry extracts would be effective in reversing age-related deficits in neuronal and behavioral function in aged (19 months) rats.
Hypothesis diagram	Increase in dietary antioxidant levels → decrease OS → reversing age-related deficits
Experimental diets or reagents	1.48% strawberry extract;(0.91% spinach extract); 1.86% blueberry extract (w/v) added to a control diet of modified AIN-93 diet.
Control diets or reagents	Modified AIN-93
Study characteristics	Country: US Funding source: supported by the US Department of Agriculture
Gap in Knowledge	Known: Unknown:
Experimental model	Fischer 344 rats had been shown to exhibit decrements by 15 months of age.
Study design	19 month old Fischer 344 rats; 4 groups; each group was fed a different diet for 8 weeks; then was given the experiments.
Final sample size	Control 10 rats; strawberry 10; blueberry 10
Duration	8 weeks
Measurements / Endpoints / Outcomes of interest	A battery of age-sensitive tests of psychomotor behavior was administered in a randomized order. Each test was performed once, separated by no less than a 1 hr break between tasks. The tests included rod walking; wire suspension; plank walking; inclined screen and accelerating rotarod. Cognitive testing used the working memory version of the Morris water maze. It was performed daily for 4 consecutive days, with a morning and an afternoon session, two trials (trial 1 and trial 2) each session, with a 10 min intertrial interval. Dopamine release GTPase activity: all striatal slices Ca^{2+} recovery were examined in the striatal synaptosomes Analyses of oxidative stress
Other outcomes reported	Vitamin E analyses
Results	Psychomotor behavior: Significant effects of diet on rod walking ($p<0.05$) and the accelerating rotarod (<0.05). For the rod walk, latency to fall was significantly longer in the blueberry groups compared to control ($p<0.01$) and strawberry ($p<0.01$) compared to control For the accelerating rotarod, latency to fall was longer in the blueberry group compared to the strawberry ($p<0.05$) group, and tended to be higher than the control group ($p=0.06$). There was no effect of diet group on wire suspension, inclined screen, or any measure of plank walking. Cognitive testing: ANOVA showed no effects of diet for either trial 1 or trial 2 performance on latency, distance, or speed. However, when separate t tests were performed between the two trial latencies for each diet, positive effects of diet supplementation were observed. For latency to find the platform on days 3 and 4, the strawberry ($p<0.05$), and blueberry ($p<0.01$) groups showed significant differences between trial 1 and trial 2, i.e. trial 2 latencies were significantly less than trial 1. This one-trial learning was not found in the control group. For distance swam to the platform on days 3 and 4, similar results were found, strawberry ($p<0.05$), blueberry ($p<0.01$) groups showed significant improvements between trial 1 and trial 2, with trial 2 distances significantly less than trial 1. No significant improvement was seen in the control group.

	Dopamine release: All striatal slices obtained from the animals in the various diet groups (6 animals per group) showed significantly greater oxotremorine-enhanced striatal dopamine release then that seen in those obtained from animals maintained on the control diet (control versus strawberry $p<0.0001$, control versus blueberry $p<0.0001$). Additional *post hoc* comparisons indicated that oxotremorine-enhanced dopamine release in the blueberry-fed group was greater than that seen in the strawberry-fed ($p<0.0001$) group. GTPase activity: Age-induced decrements in carbachol stimulated GTPase activity were significantly less with blueberry ($p<0.0001$) but not strawberry ($p>0.05$) than control. Oxidative stress: In the striatum, only the strawberry group ($p<0.002$) and blueberry ($p<0.005$) groups showed greater native OS protection than control group. Stawberry diet had greater ^{45}Ca recovery ($p<0.001$), whereas the blueberry diet had lower recovery ($p<0.05$), in non-H_2O_2-treated synaptosomes compared to the control diet. After treatment with 300 μM H_2O_2 only the blueberry group showed greater ^{45}Ca recovery ($p<0.05$) after treatment, i.e., a greater ability to extrude or sequester calcium after depolarization, than the control group. In fact, after exposure to H_2O_2 only the blueberry-fed diet group had no deficits in ^{45}Ca recovery.
Authors' Conclusions	Supplementation with the blueberry extract improved motor performance on 2 motor tests that rely on balance and coordination. These rats demonstrated one-trial learning, even with the 10 min retention interval.
Quality	A
Limitations / Comments	The amounts of strawberry and blueberry extracts added into the control diet were based on an equivalent ORAC activity so that each diet provided equivalent antioxidant activity.

Author, Year	Shukitt-Hale, 1999
Central hypothesis/Stated Purposes of Study	To determine the efficacy of dietary supplementation with antioxidants in reversing/restoring age-related declines in motor performance in mice
Hypothesis diagram	
Experimental diets or reagents	Freeze-dried aqueous strawberry extract (1%)
Control diets or reagents	Modified AIN76 diet with 30 ppm Vit E
Study characteristics	Country: US Funding source: No data
Gap in Knowledge	Known: Oxidative stress (OS) is thought to be a contributing factor to the decrements in motor performance seen in aging. Antioxidant nutrients added to the diet are one defense strategy to prevent, intercept, or repair age-induced OS. Vitamin E, glutathione (GSH), melatonin, and strawberry extract have all been found to have antioxidant properties. Unknown:
Experimental model	Male C57BL.6NIA mice, 18 months of age before the dietary treatments.
Study design	Randomized control trial: weight matched mice were randomly assigned to 1 of 6 diet groups. An untreated group (n=11) of 4-month-old mice served as young, chow-fed, controls.
Final sample size	Weight-matched dataset: Control: 8 Strawberry: 10
Duration	6 months
Measurements / Endpoints / Outcomes of interest	Behavioral testing: a battery of psychomotor behavioral tests was performed that consisted of complex movement tasks, which have been shown to deteriorate with age. The tests included: 1) Rod walking, 2) Wire suspension/wire hanging, 3) Plank walking; 4) Inclined screen
Other outcomes reported	Body weight
Results	For control rats only, several tests showed deficits from 4 to 18 months; however, no tests showed additional performance decrements from 18 to 24 months. Specifically, in the rod walking test and wire-hang test, ANOVA showed a significant age difference ($p<0.01$); post-hoc testing showed that latency to fall was longer for the young group than for the 18-month ($p<0.01$) or the 24-month group ($p<0.01$). Only data from the 4- and 24-month groups were comparable for the inclined screen, as both of these group were tested at the 85º angle (60º angle proved too easy for the mice as they all achieved max time regardless of age or diet), there was a significant age effect on the inclined screen ($p<0.01$), with the 24-month-old animals having a shorter latency to fall than the 4 –month-group. There were no age differences for plank walk latency, distance, or turns. There was no significant difference in the any parameter (when analyzing the weight-matched dataset) between strawberry-fed and control animals.
Authors' Conclusions	Although some deficits were seen from 4 to 18 months, motor performance for the 18-month group on all measures was never different from the 24-month group.
Quality	A
Limitations / Comments	To control for the difference in body weight and prevent its influence on the behavioral tests, subsequent ANOVAs were run on a subset of the animals by discarding mice with a weight of greater or less than 1 standard deviation away from the mean weight of all the mice. A total of 32 mice were eliminated from the analyses.

Author, Year	Bickford, 2000
Central hypothesis/Stated Purposes of Study	Combinations of nutrients in foods with high antioxidant activity may reverse the age-related behavioral and neurochemical deficits in older rats. High antioxidant foods may improve cerebellar β-adrenergic receptor function, thus improving cerebellar motor learning in older rats.
Hypothesis diagram	Combinations of nutrients in foods with high antioxidant activity →↑cerebellar β-adrenergic receptor function →↑motor learning
Experimental diets or reagents	Strawberry diet: control diet supplemented with strawberry extracts (14.8 g/kg dried aqueous extract) Blueberry diet: control diet supplemented with blueberry extracts (18.6 g/kg dried aqueous extract)
Control diets or reagents	Modified AIN-93 (Detailed composition listed in Table 1)
Study characteristics	Country: US Funding source: supported by the US Department of Agriculture, Veterans Administration Medical Research Service, and US Public Health Service
Gap in Knowledge	Known: Combinations of nutrients in foods with high antioxidant activity delay age-related behavioral and neurochemical deficits in young rats. Unknown: Whether high anti-oxidant diet at a later age would reverse the age-related deficits in behavior and β-adrenergic receptor function in the cerebellum.
Experimental model	Male Fischer (F344) rat, 18 months of age
Study design	Parallel comparative study
Final sample size	30 (14 control, 8 blueberry, 8 strawberry)
Duration	8 weeks, from age 18 to 20 months
Measurements / Endpoints / Outcomes of interest	Motor learning: Time to cross runway of variably placed rods. 1) Actual time (% of initial running time); 2) Decay constant (slope, rate of learning of the task). Extracellular electrophysiologic recordings of cerebellar Purkinje neurons for potentiation of GABAergic inhibition by the β-adrenergic ISO (post-mortem)
Other outcomes reported	Total glutathione levels in the cerebellum (post-mortem)
Results	Motor learning: 1. No significant difference in asymptote (percent of initial running time after 10-14 days) between blueberry or strawberry compared to control diets. 2. Trend toward faster learning (steeper decay constant [slope], p=0.15) in blueberry diet rats compared to control (non-significant). (However, strawberry-fed rats were faster than controls at baseline, thus they did not have a steep learning curve.) Electrophysiologic recording: ISO potentiation of GABAergic inhibition in the cerebellum in observed in a significantly higher percentage of neurons recorded from the blueberry- ($p<0.001$) and strawberry-fed ($p<0.05$) groups as compared to control.
Authors' Conclusions	Diets high in antioxidants can improve performance on a motor learning task and reverse an age-induced decline in cerebellar β-adrenergic receptor function. The improvement in speed during the first few days for the strawberry and blueberry fed rats might be due to improved psychomotor performance as opposed to improved motor learning; however an effect on learning within the first training session would not be detected. Further experiments are required to investigate the effects of the various phytochemicals found in these foods.
Quality	
Limitations / Comments	The amounts of strawberry and blueberry extracts added into the control diet were based on an equivalent ORAC activity so that each diet provided equivalent antioxidant activity.

Author, Year	Martin, 2000
Central hypothesis/Stated Purposes of Study	(1) to analyze the long-term (8 months) effect of low vitamin E in brain and other tissues; (2) to examine the brain's vitamin E distribution following dietary vitamin E treatment; (3) to determine if low vitamin E intake could affect vitamin C synthesis to compensate for the vitamin E deficit; and (4) to determine function and attenuate the deleterious effects associated with aging without affecting the concentrations of vitamins E and C
Hypothesis diagram	Antioxidants from fruits and vegetables → reduction of oxidative stress → prevention of neurodegenerative diseases
Experimental diets or reagents	Strawberry exact (9.5 g/kg diet), [spinach (6.4 g/kg diet), or vitamin E (with 500-mg all-rac-α-tocopheryl acetate/kg diet)] added to the control diet
Control diets or reagents	Modified AIN-93
Study characteristics	Country: US Funding source: ND
Gap in Knowledge	Known: Age-related neurological deterioration is accompanied by a significant decrease of transmitter levels as well as activity of neurotransmitter-synthesizing enzymes. Unknown: Antioxidants may play in preventing oxidative damage and their application in the prevention of neurodegenerative diseases.
Experimental model	6-month-old male Fischer 344 rats (Harlan Sprague Dawley, Indianapolis, IN) were used. When testing, all rats were at the age of 15 months.
Study design	Following a 12-day acclimatization period to the facility, the 6-month-old male Fischer 344 rats (were weight-matched and given 2 weeks on the control diet. They were then divided into 4 diet groups (control, strawberry extract, spinach extract and high vitamin E groups). [Note: for the purpose of this report, only control and strawberry extract groups are of interest.]
Final sample size	Ctrl 20 Strawberry 20
Duration	8 months
Measurements / Endpoints / Outcomes of interest	Dopamine release
Other outcomes reported	Weight and food intakes Vitamins E and C levels in brain (hippocampus, cerebellum, and striatum), plasma, in liver, and in heart
Results	Diets enriched with extracts of strawberry showed enhanced dopamine release from striatal slices following oxotremorine stimulation by 100% compared to control ($p<0.05$)
Authors' Conclusions	The observation that dopamine release induced by the diets containing strawberry was significantly enhanced compared to control diet is important, because brain tissues from control and experiment animals had very low vitamin E, compared to the high-vitamin-E group suggesting that other nutrients may be important for maintaining brain's function.
Quality	B
Limitations / Comments	No behavioral or cognitive function outcomes

Author, Year	Youdim, 2000
Central hypothesis/Stated Purposes of Study	Blueberry supplementation diet prevents the cognitive decline through decreasing the susceptibility to OS; and may have benefits in peripheral systems.
Hypothesis diagram	1) BB supplementation diet → decrease susceptibility to OS, ?dopamine release → decrease cognitive decline 2) BB supplementation diet → increase aminotransferase (AST) activity - - - -> benefits in peripheral tissue function
Experimental diets or reagents	Blueberry (BB) supplemented diets: 2% of the control diet was supplemented with either wild blueberry or tif-blue blueberry extract. Overall this was equivalent to the consumption of 4 g of BB (1 kg of whole BB yielded 110 g of BB extract, assuming that rats consumed approximately 20 g diet/day).
Control diets or reagents	Control diet specification was described in Table 1
Study characteristics	Country: US Funding source: ND
Gap in Knowledge	Known: Previous studies showed that rats maintained on diets enriched with strawberry or spinach extracts for 8 months exhibited less age-related deficits in neuronal signal transduction and cognitive behavior impairment. Unknown: If the beneficial effects can be observed when using a well-balanced chow diet that already contained sufficient levels of vitamin E, and which overall was more comparable with a normal balanced human diet.
Working model	17-month Male Fisher 344 rats (Harlan Sprague Dawley, Indianapolis, IN)
Internal standard	6-week run-in control chow diet
Study design	RCT of control, tif-blue blueberry (tif-BB) and wild blueberry (wild BB) diets. 15 rats per groups.
Final sample size	Control: 12 tif-BB:13 Wild-BB: 14
Duration	8 weeks
Measurements / Endpoints / Outcomes of interest	Age-sensitive tests of psychomotor behavior: 1) Rod walking, 2) Wire suspension, 3) Plank walking, 4) Inclined screen; 5) Accelerating rotarod Cognitive testing: Morris water maze, latency to find the platform, distance swam, and speed, were calculated separately for Trials 1 and 2. Performance was assessed over 4 days (2 sessions/day, 2 trials/session) Dopamine release
Other outcomes reported	Erythrocyte ghost membrane fluidity RBC susceptibility to OS insult: dichlorofluorescein (DCFH-DA) assay Flavonoid extraction from plasma
Results	Tests of psychomotor behavior: Tif-BB → latency to fall was significantly longer compared to on the inclined screen ($p=0.06$) and the large plank ($p<0.05$), but no significant difference in the accelerating rotarod testing. Wild-BB → latency to fall was significantly longer compared to control on the accelerating rotarod ($p<0.05$) and the large plank ($p<0.05$), but no significant difference in the inclined screen testing. Morris water maze: Tif-BB → significantly lower latency to find the platform on Trial 1 ($p<0.05$) but the latency was not different on Trial 2 Wild-BB → no significant difference in the latency to find the platform on both Trial 1 and 2 Dopamine release: Both Tif-BB ($p<0.05$) and Wild BB ($p<0.05$) supplemented animals showed significantly greater oxotremorine-enhanced striatal dopamine release than control animals, but they were not differ from each other.
Authors' Conclusions	Supplementation with the BB extract improved performance on motor tests, and enhanced striatal dopamine release. Tif-BB supplementation improved reference memory performance (Trial 1 only), but not wild-BB supplementation.
Quality	A
Limitations / Comments	The effects on improving memory performance were weak.

Author, year	Joseph, 2003
Central hypothesis/Stated Purposes of Study	Blueberry supplementation may be of benefit in reducing the symptomology of Alzheimer's disease (AD)
Hypothesis diagram	BB suppl → increase GTPase, decrease N-Sase, ?PKC; ?ERK → improve Y-maze performance; less Aβ deposition in the brain
Experimental diets or reagents	Blueberry (BB) supplemented diet: 2% of the control diet was supplemented with BB extract from 4 months through 12 months of age
Control diets or reagents	Control diet (modified NIH-31) specification was described in Table 1
Study characteristics	Country: US Funding source: ND
Gap in Knowledge	Known: 1) significant reductions in muscarinic receptor –G protein signaling as a function of AD and aging; 2) increase in neutral sphingomyeline-specific PLC (N-Sase) activity with age Unknown: other signaling parameter associated with aging, e.g. calcium-dependent protein kinase C (PKC), extracellular signal regulated kinase (ERK)
Experimental model	Mice transgenic for amyloid precursor protein (APP) and presenilin-1 (PS1) mutations. These mice are prone to fibrillar Aβ deposits in cerebral cortex and hippocampus early in the life-span with later changes in cognitive behavior
Study design	Transgenic vs. non-transgenic mice (CTR-N), both groups on either blueberry diet (BB) or control diet (Control)
Final sample size	Transgenic BB 3 CTR-N BB 7 Transgenic Control 3 CTR-N Control 8
Duration	12 months
Measurements / Endpoints / Outcomes of interest	Y-maze performance Fibrillar Aβ deposits in the brain Brain neutral sphingomyelin-specific phospholipase C (N-Sase) activity Brain low Km GTPase activity Brian calcium-dependent protein kinases (PKC) activity: protein kinase Cγ (PKCγ); phospho-protein kinase Cα Brian extracellular regulated signal kinases (ERK) activity
Other outcomes reported	
Results	BB supplementation had a beneficial effect on Y-maze performance in transgenic mice, as demonstrated by higher percentages of alternation behavior [p<0.05] There is no significant difference I the Y-maze performance between the wild-type mice fed blueberry diet and those fed control diet. BB supplemented transgenic mice had no change on Aβ deposits in the brain BB supplementation significantly increased the low Km GTPase activity (p<0.05) in striatum but not in hippocampus or cortex in transgenic animals compared to the respective controls. No significant effects of BB supplementation was found in non-transgenic animals. Positive correlation between GTPas activity and Y-maze alternation in the striatum but not in the hippocampus or cortex BB supplementation significantly decreased N-Sase activity for both transgenic animals (p<0.01) and controls (p<0.01) in the striatum, hippocampus, and the cortex. Negative correlation between N-Sase activity and Y-maze alternation in the striatum but not in the hippocampus or cortex BB supplementation increased hippocampal ERK activity in the transgenic mice (p<0.001). Other brain regions were not examined. Correlation between hippocampal ERK activity and Y-maze alternation did not reach significance. The levels of PKCγ were unaffected by the transgenic condition or the diet (data not shown) in any of the brain regions examined and the correlations between this parameter and Y-maze alternation were not significant. BB supplementation increased hippocampal phospho-PKCα activity in the transgenic mice (p<0.05). No differences were seen in

	other brain areas among the various groups. Correlational analyses with Y-maze performance revealed a trend toward significance in the hippocampus (p=0.09)
Authors' Conclusions	BB suppl → increase GTPase (yes in striatum, p<0.05), decrease N-Sase (yes in striatum and hippocampus, p<0.01), PKC (no effect); ERK (increase in hippocampus, p<0.01) → improve Y-maze performance (yes, p<0.05); less Aβ deposition in the brain (no) Although BB supplementation did not affect Aβ deposits, the supplementation seemed to have prevented the deficits in Y-maze performance seen in the transgenic animals fed the control diets.
Quality	A
Limitations / Comments	Transgenic mice should have lower Y-maze performance, lower GTPase activity, higher N-Sase activity compared to CTR-N mice when feeding control diet (data were shown). Correlate the "intermediate markers" to the neurocognitive measures!

Author, Year	Casadesus, 2004
Central hypothesis/Stated Purposes of Study	To examine whether neurogenesis, growth factors, and mitogen-activated protein-kinase (MAPK), in combination or synergistically, were associated with improvements in hippocampally-dependent cognitive output in aged blueberry-supplemented rats
Hypothesis diagram	Blueberry supplementation → ? neurogenesis, ? growth factors ? MAPK → improve cognitive output
Experimental diets or reagents	Blueberry extract diet: 2% of the control diet was supplemented with blueberry extract. Overall this was equivalent to the consumption of 4 g of BB (1 kg of whole BB yielded 110 g of BB extract, assuming that rats consumed approximately 20 g diet/day).
Control diets or reagents	NIH-31 20g/kg
Study characteristics	Country: US Funding source: No data
Gap in Knowledge	Known: Dietary fruit and vegetable supplementation appear to forestall or reverse various age-related neuronal declines. Unknown: The mechanisms responsible for behavioral and neuronal changes seen during aging are not fully understood.
Experimental model	19-month-old male F344 rats (Harlan Sprague-Dawley, Indianapolis, IN)
Study design	RCT
Final sample size	10 in total (assumed 5 per group)
Duration	8 weeks
Measurements / Endpoints / Outcomes of interest	Radial Arm Water Maze (RAWM) performances: rats were tested for 5 consecutive days. The order of entry into the maze arms was recorded so that the number of errors could be analyzed. The errors recorded were reference (long-term) memory errors (defined as entering an arm that disen't contain the platform) and working (short-term) memory errors (defined as the animal re-entering an already visited arm whether or not it contained the platform). Total memory errors refer to the addition of reference and working memory errors. Neurogenesis in the rat brain: bromodeoxyuridine (BrdU) incorporation into the nuclei of dividing cells and co-localized with the glial marker primary antiglial fibrillary acidic protein (GFAP) antibody to exclude the presence of glial BrdU labeling Hippocampus growth factors, such as IGF-1 and IGF-1R levels, and extracellular-signal-regulated-kinase (ERK) activation
Other outcomes reported	
Results	RAWM performances: Repeated measures analysis across days revealed a significant day effect for latency ($p<0.0001$) suggesting that rats in both groups could successfully learn the task on days 1-3. The lack of interaction between groups ($p<0.744$) suggested that the rate of learning on days 1-3 did not differ across groups. On day 4, compared to animals fed the control diet, blueberry-fed rats had significantly fewer reference memory errors ($p<0.05$) and total memory errors ($p<0.05$), and also showed a trend towards fewer working memory errors ($p<0.06$). No significant difference in RAWM performances was seen between groups on day 5. Neurogenesis: Short-term blueberry supplementation significantly increased proliferation of precursor cells in the dentate gyrus of aged rats ($p<0.05$). Pearson's correlations revealed that, as the number of proliferating cells increased, the number of memory errors on Day 4 decreased (reference memory errors: r=-<0.684, $p<0.05$; working memory errors: r=-<0.646, $p<0.05$; total memory errors: r=-<0.677, $p<0.05$). IGF-1 and IGF-1R levels: A significant increase in the levels of IGF-1 protein by blueberry supplementation compared to the control rats ($p<0.001$). Increased IGF-1 levels were associated with significant decreases in memory errors (total memory errors: r=-0.626, $p<0.05$). and trends towards decreased reference memory errors (r=-0.539, $p<0.09$) and working memory errors (r=-0.581, $p<0.07$). There was a statistically significant positive correlation between ERK activation and IGF-1 levels (r=0.748, $p<0.05$). There were no significant correlations between levels of IGF-1 and proliferation.

	Levels of IGF-1R in blueberry-supplemented rats were significantly increased compared to the control rats ($p<0.05$), and correlated with levels of IGF-1 ($r=0.788$, $p<0.01$). The increase in IGF-1R were associated with decreases in total memory errors ($r=-0.375$, $p<0.05$) and reference memory errors ($r=0.738$, $p<0.01$) but not working memory errors ($r=-0.545$, $p<0.104$) on day 4. There was a statistically significant positive correlation between ERK activation and IGF-1R levels ($r=0.722$, $p<0.05$) but not proliferation. ERK activation: There was a significant increase of ERK activation by blueberry supplementation ($p<0.01$). The increase in ERK activation were related to decreases in total memory errors ($r=-0.629$, $p<0.05$) and reference memory errors ($r=-0.636$, $p<0.05$) but not working memory errors ($r=-0.537$, $p<0.109$) on day 3. Proliferation was not significantly correlated with ERK activation.
Authors' Conclusions	Blueberry supplementation → increase IGF-1, IGF-1R, and ERK activation → decreases in total memory errors and reference memory errors but NOT working memory errors on day 4 Increase IGF-1, IGF-1R, and ERK activation are NOT associated with neurogenesis Blueberry supplementation → increased proliferation of precursor cells in the dentate gyrus of aged rats → decreases in total memory errors, reference memory errors, and working memory errors
Quality	A
Limitations / Comments	Correlate the "intermediate markers" to the neurocognitive measures!

Author, Year	Goyarzu, 2004
Central hypothesis/Stated Purposes of Study	(1) Aged rats on control diet will be impaired in object recognition memory, (2) The age-related impairment will be more severe with a longer delay between object presentation and preference testing (maximizing memory demand), (3) Aged rats on control diet will have elevated cytosolic NF-kB levels in several brain regions, (4) For months of diet supplementation with antioxidant-rich blueberry extract will significantly reduce both the age-related memory impairment and the elevation of NF-kB
Hypothesis diagram	Supplementation of blueberry extract → reduced the elevation of NF-kB (a indicator of oxidative stress) → reduced age-related memory impairment
Experimental diets or reagents	2% blueberry supplemented to NIH-31 rodent chow. 200 g/week.
Control diets or reagents	2% dried corn supplemented to NIH-31 rodent chow. 200 g/week.
Study characteristics	Country: US Funding source: University funded
Gap in Knowledge	Known: The protein transcription factor, nuclear factor-kappa B (NF-kB) is a highly responsive indicator of oxidative stress (OS). Increased NF-kB activity may constitute a protective response, buffering the effects of OS as induction of apoptosis and mitochondrial dysfunction. Unknown:
Experimental model	Aged subjects: 15-month-old male virgin Fischer-344 rats (19-months old at time of testing) Young subjects: 4-month-old male virgin Fischer-344 rats (8-months old at time of testing)
Study design	For 4 months prior to testing, 12 young rats were maintained on the control diet. 12 aged rats were maintained on the control diet, while 12 aged rats were fed the BB-supplemented diet.
Final sample size	Young Ctrl: 12 Aged Ctrl: 12 Aged BB: 12
Duration	4 months
Measurements / Endpoints / Outcomes of interest	Object recognition memory: Ennaceur and Delacour (1988) introduced a non-spatial object recognition memory task that test a rat's recognition memory for having previously encountered and explored an object. The procedure exploits the innate tendency of rats to preferentially explore novel vs. familiar objects. Young rats spend much more time closely exploring the novel object than the familiar object. NF-kB levels in the brain: 4 days after the conclusion of behavioral testing, subjects were perfused with saline, Brains were removed and dissected into 3 different regions, including the frontal cortex, hippocampus, basal forebrain, striatum and cerebellum.
Other outcomes reported	Weight gain
Results	Object recognition memory: All 3 groups showed significantly greater than chance preference for the novel object with a 30-s training-test delay, but only in the young rats and the BB diet aged rats with a 1-h delay. Pair-wise post-hoc comparisons (Fisher's LSD test) of object recognition scores after the 30-s delay revealed no significant differences among the 3 groups. Pair-wise post-hoc comparisons of object recognition scores after the 1-h delay revealed that young rats had significantly higher object recognition memory scores than aged rats on the control diet ($p<0.01$). The blueberry-supplemented aged rats also had significantly higher object recognition memory scores than aged rats on the control diet ($p<0.01$). There is no significant difference between the young rats and the blueberry-supplemented aged rats. NF-kB levels in the brain: In every region, aged rats maintained on the control diet had higher NF-kB levels than young rats maintained on the control diet. In every region, aged rats maintained on the BB-enriched diet had lower NF-kB levels than aged rats maintained on the control diet. In all regions except the basal forebrain, this difference was significant.

	In the cerebellum, the aged rats maintained on the BB-enriched diet had significantly higher NF-kB levels than the young rats. However, in the other 4 regions, there was no significant difference between those 2 groups.
Authors' Conclusions	Blueberry supplementation eliminated the deficit in 19-month old rats, in that the aged the aged blueberry-supplemented rats, not only performed significantly above chance, but also performed as well as young rats. Blueberry supplementation attenuates the elevation of NF-kB levels in the aging rat brain.
Quality	A
Limitations / Comments	

Author, Year	Joseph, 2004
Central hypothesis/Stated Purposes of Study	Blueberry and other fruit extracts may provide protection against Aβ 25-35 or dopamine (DA) in the COS-7 cell model.
Hypothesis diagram	Fruit extracts → reduce Aβ (25-35)- or DA- induced oxidative stress (OS) through MAChRs
Experimental diets or reagents	2 mg/ml blueberry (BB), 2 mg/ml black currant (BC), 2 mg/ml boysenberry (BY), or 0.5 mg/ml strawberry (SB), 1 mg/ml cranberry (CB) pre-treatments
Control diets or reagents	No pre-treatments
Study characteristics	Country: US Funding source: No data
Gap in Knowledge	Known: The effects of OS may occur at the receptor level. In this respect, experiments have shown that there is a loss of sensitivity in MAChRs as a function of age and AD, as well as aging. Recent findings have shown that COS-7 celss transfected with one of the 5 MAChRs and exposed to DA showed differences in OS sensitivity in calcium buffering. In 2 previous experiments, it was shown that antioxidants can prevent the loss of viability in COS-7 cells transfected with sensitive (M1AchR) muscarinic receptors and exposed to DA, and prevent the decrease in Recovery in M1AchR-transfected COS-7 cells exposed to Aβ (25-35, 100 μM). Unknown: if similar protection (described above) could be achieved against Aβ (25-35, 100 μM) or DA exposure in M1AchR-transfected COS-7 cells following pre-treatment with various fruit extracts that have high antioxidant activity.
Experimental model	COS-7 cells (ATCC) transfected with rat muscarinic receptor subtype 1 or 3 DNA by the DEAE-dextran method
Study design	In vitro: Each fruit extract was dissolved in growth media and M1AchR-transfected COS-7 cells were subsequently incubated for 45 min at 37 °C with the treated growth medium. Following these incubations the cells were washed 3 times with extract-free growth medium prior to testing. Note that no repeated measures were utilized in these studies.
Final sample size	N/A
Duration	N/A
Measurements / Endpoints / Outcomes of interest	Ca^{2+} Recovery following 0 or 1 mM DA treatment: Recovery was determined by assessing the time (within 300 sec) for the Ca^{2+} level to return to 20% of the increase following depolarization in the cells that responded. Ca^{2+} Recovery following 0 or 100 μM Aβ (25-35) treatment % Viability following 0 or 1 mM DA treatment: Viability of the cell at 24 hrs following a 4 hr exposure to 1 mM DA was determined using the Live/Dead Eukolight Viability/Cytotoxicity Kit (Molecular Probes, Eugene, OR) without detaching the cells from the 35 mm plates.
Other outcomes reported	
Results	In the absence of pre-treatment (control condition) there were significant effects of both DA and Aβ on Recovery of the M1-transfected cells (e.g., control vs. DA- or Aβ-treated cells with no extract pre-treatment, $p<0.001$). In comparisons with the non-preteated DA-exposed cells, all of the fruit extract pre-treatments were effective in offering some protection. However, compared to their own respective controls (not exposed to DA) only BB, and BY were totally protective against the DA. The BB-pre-treatment was the most effective in protecting against the effects of Aβ on Recovery (e.g., BB+Aβ vs. BB control, $p>0.05$; BB+Aβ vs. control, $p>0.05$; BB+Aβ vs. Aβ, $p<0.05$). The Recovery in the BC+Aβ cells did not differ from their respective controls ($p>0.05$), while the cells pre-treated with BY and exposed to Aβ showed lower Recovery than their respective controls ($p<0.05$). SB did not offer protection against Aβ and the cell exposed to Aβ and pre-treated with SB showed lower Recovery than their respective controls ($p<0.05$). BB and BY showed the strongest effects in protecting the DA-treated cells against loss of viability (e.g., BB+Aβ treated vs. non-DA,

	non-BB-treated, p>0.05). The effects of the other extracts (i.e., CB, BC, and SB) were similar except that the DA-exposed cells pre-treated with these extracts showed lower viability than that seen in their respective non-DA treated controls.
Authors' Conclusions	The results from the present study indicate that it may be possible to reduce both the deleterious effects of DA and the putative toxic effects of Aβ via fruits high in antioxidant activity. Each of these fruit extracts showed some degree of protection against the deleterious effects of DA on Recovery, with SB showing the weakest effects. The most efficacious extracts were BB and BY which were totally protective against the effects of DA, as compared to their own respective controls. BB pre-treatment was also the most beneficial in protecting against the effects of Aβ on Recovery, while, unlike the effects seen with DA, BC exceeded those of BY and GR effects were negative. As with DA exposure, SB showed very little protective effect against Aβ on Recovery. In the case of Viability, the M1-transfected COS-7 cells showed similar effects to that seen with respect to Recovery, with BB and BY showing the strongest effects.
Quality	B
Limitations / Comments	The study also had 0.5 mg/ml dried plum and 0.05 mg/ml grape (GR) pre-treatments but they are not of interest to this report. Note that no repeated measures were utilized in these studies.

Author, Year	Rabin, 2005A
Central hypothesis/Stated Purposes of Study	To evaluate the effects of strawberry and blueberry supplementation on operant performance in rats exposed to 1.5 Gy of ^{56}Fe particles. Specifically, (1) would antioxidant diets be equally effective following exposure to a higher dose of heavy particles, which presumably produce a greater level of oxidative stress? (2) What would be the nature of the interaction with the age of the animal at the time of testing?
Hypothesis diagram	Heavy particle irradiation → neurobehavioral deficits due to accelerated oxidative stress. Berry antioxidants may be protective.
Experimental diets or reagents	Blueberry (BB) diet: 2% of the control diet was supplemented with blueberry extract. Overall this was equivalent to the consumption of 4 g of BB (1 kg of whole BB yielded 110 g of BB extract, assuming that rats consumed approximately 20 g diet/day). Berry homogenate replaced corn in NIH-31 diet. Strawberry (SB) diet: 2% of the control diet was supplemented with strawberry extract.
Control diets or reagents	NIH-31
Study characteristics	Country: US Funding source: National Aeronautics and Space Administration (NASA)
Gap in Knowledge	Known: Exposure to heavy particles such as ^{56}Fe produces deficits in neurobehavioral function which are characteristic of the aged organism. Unknown: Whether high anti-oxidant diet, in the form of blueberries or strawberries, can mitigate effect of radiation
Experimental model	Male Sprague-Dawley rats weighing 175-200 g
Study design	Rats were placed on a diet containing blueberry extract, or strawberry extract, or on a control diet for 2 months prior to irradiation. The rats were irradiated with 1.5 Gy of ^{56}Fe. After exposure the rats were trained and tested on the operant task. After exposure, all rats were placed on non-berry supplement diets.
Final sample size	BB+^{56}Fe: 10 SB+^{56}Fe: 10 Ctrl+^{56}Fe: 10 BB: 10 SB: 10 Ctrl: 10 Several rats, particularly among those irradiated & on control diet, were euthanized before completion due to tumor development
Duration	12 months after irradiation
Measurements / Endpoints / Outcomes of interest	Operant task: The rats were food deprived to 85%-90% of their base weight and trained to lever press for a 45-mg food pellet using an autoshaping procedure, which was followed by training to respond on an Fixed-Ratio (FR) reinforcement schedule. Once this response had been acquired, the rats were immediately tested on an ascending FR schedule for FR-1 to FR-35. 2 replications were carried out at 6 and 12 months postirradiation.
Other outcomes reported	
Results	When tested 6 months after irradiation, all groups, irrespective of diet or irradiation status performed equally. At 12 months after irradiation, irradiated rats fed strawberries performed equally well as non-irradiated rats. Irradiated rats fed blueberries or control diet performed equally poorly compared to the other groups.
Authors' Conclusions	Disruption of operant performance (specifically response to an ascending fixed ratio schedule) by heavy particle irradiation in older rats can be prevented by maintaining rats on a diet containing 2% strawberry extract, but not blueberry extract. Lack of difference among diets and radiation status at 6 months was expected from previous research indicating that the deleterious effects of exposure to 1.5 Gy of ^{56}Fe particles occurs among older rats.
Quality	A
Limitations / Comments	Unclear whether exposure to heavy particles is an appropriate model for human neurocognitive disease while on Earth.

Medline UI 15725409

Author, Year	Rabin, 2005B
Central hypothesis/Stated Purposes of Study	To evaluate the effects of strawberry and blueberry supplementation on operant performance in rats exposed to 2.0 Gy of ^{56}Fe particles. Specifically, (1) would antioxidant diets be equally effective following exposure to a higher dose of heavy particles, which presumably produce a greater level of oxidative stress? (2) Would the previously obtained difference in the effectiveness of the strawberry diet compared to the blueberry diet be observed in an independent experiment using a higher dose of radiation? (3) What would be the nature of the interaction with the age of the animal at the time of testing?
Hypothesis diagram	Heavy particle irradiation → neurobehavioral deficits due to accelerated oxidative stress. Berry antioxidants may be protective.
Experimental diets or reagents	Blueberry (BB) diet: 2% of the control diet was supplemented with blueberry extract. Overall this was equivalent to the consumption of 4 g of BB (1 kg of whole BB yielded 110 g of BB extract, assuming that rats consumed approximately 20 g diet/day). Strawberry (SB) diet: 2% of the control diet was supplemented with strawberry extract.
Control diets or reagents	NIH-31
Study characteristics	Country: US Funding source: National Aeronautics and Space Administration (NASA)
Gap in Knowledge	Known: Exposure to heavy particles such as ^{56}Fe produces deficits in neurobehavioral function which are characteristic of the aged organism. Deleterious effects mitigated by X diet after 1.5 Gy irradiation Unknown: Effect of berry diets after higher dose irradiation.
Experimental model	Male Sprague-Dawley rats weighing 175-200 g
Study design	Rats were placed on a diet containing blueberry extract, or strawberry extract, or on a control diet for 2 months prior to irradiation. The rats were irradiated when they were about 3.5 to 4.0 months of age with 2.0 Gy of ^{56}Fe. Following exposure the rats were trained and tested on the operant task. After exposure, the rats were fed a diet of standard lab chow (Purina 5100).
Final sample size	BB+^{56}Fe: 8 SB+^{56}Fe: 8 Ctrl+^{56}Fe: 8 BB: 4 SB: 4 Ctrl: 8 Several rats, particularly among those irradiated & on control diet, were euthanized before completion due to tumor development
Duration	18 months after irradiation
Measurements / Endpoints / Outcomes of interest	Operant task: The rats were food deprived to 85%-90% of their base weight and trained to lever press for a 45-mg food pellet using an autoshaping procedure, which was followed by training to respond on an Fixed-Ratio (FR) reinforcement schedule. Once this response had been acquired, the rats were immediately tested on an ascending FR schedule for FR-1 to FR-35. 4 replications were carried out: 5, 8, 13 and 18 months postirradiation.
Other outcomes reported	
Results	Significant interactions were found between diet (combined berry vs control), irradiation (vs non-irradiation), and testing replication time (5, 8, 13, and 18 months after irradiation and initial training, i.e., age). When tested 5 and 8 months after irradiation (9 and 12 months of age), irradiated rats fed strawberries performed equally well as non-irradiated rats. Irradiated rats fed blueberries or control diet performed equally poorly compared to the other groups. At 13 and 18 months after irradiation, there was a decrement in the performance of the irradiated rats consuming strawberries compared to those on the blueberry diet; although their performance remained somewhat better. Comparison with irradiated rats on control diet could not be made because all but 2 of these animals died.
Authors' Conclusions	Disruption of operant performance (specifically response to an ascending fixed ratio schedule) by heavy particle irradiation can be prevented by maintaining rats on a diet containing 2% strawberry extract, but not blueberry extract. Similar to previous results found with exposure to 1.5 Gy of ^{56}Fe, except that difference between diets is found at an earlier age.
Quality	A
Limitations / Comments	Unclear whether exposure to heavy particles is an appropriate model for human neurocognitive disease while on Earth.

Not in Medline or CAB abstracts

Author, Year	Shukitt-Hale, 2005
Central hypothesis/Stated Purposes of Study	To determine whether the beneficial effects of blueberries would also be seen with other berry fruits as compared with a control diet.
Hypothesis diagram	
Experimental diets or reagents	2% of the control diet was supplemented with blueberry (BB), blackcurrant (BC), boysenberry (BS) or cranberry (CB) extracts. The anthocyanin and total phenolic concentration present in the extracts are as blow:

Berryfruit type	Total anthocyanin concentration (mg/g)	Total phenolic (325 nm) concentration (mg/g)
Blueberry	1.3	1.2
Blackcurrant	8.7	2.9
Boysenberry	9.2	2.0
Cranberry	3.3	3.6

Control diets or reagents	NIH-31 (20 g/kg)
Study characteristics	Country: US Funding source: USDA, Cranberry Institute; The Horticulture and Food Research Institute of New Zealand
Gap in Knowledge	Known: Previous studies have shown that increasing the levels of inducible hippocampal heat shock protein 70 (HSP70) can protect cells from numerous insults ranging from ischemia, inflammatory agents and reactive oxygen species. Unknown: The loss of the ability of cells to respond to these insults by increasing HSP70 may contribute to the age-related declines in both neuronal and behavioral functioning.
Experimental model	19-month-old Male Fischer 344 rats
Study design	Weight-matched rats were placed on 3 separate diets (BB, BC, BS, CB or control diets) for 13-16 weeks total
Final sample size	No data
Duration	13-16 weeks
Measurements / Endpoints / Outcomes of interest	Psychomotor testing, including (1) Rod Walk, (2) Wire Suspension, (3) Plank Walk, (4) Inclined Screen; (5) Accelerating Rotarod. Morris Water Maze (MWM), an accepted method of testing spatial learning and memory, is an age- and diet-sensitive learning paradigm that requires rats to find the location of a hidden platform just below the surface of a circular pool of water based on distal cues in previous learning trials. Hippocampal heat shock protein 70 (HSP70): in vitro LPS (Lipopolysaccharide) treatment (a stressor) Dopamine release
Other outcomes reported	
Results	Of the psychomotor testing, only the inclined screen yielded significant results between diet groups. BB (p=0.038) and CB (p=0.001) groups performed significantly better than the control group. Morris Water Maze performance showed no differences among the diet groups. Dopamine release was different among the groups. Post-hot testing found that the BC (p=0.004) and CB (p=0.007) groups were significantly better than the control and BS groups. The effects of BB supplementation on striatal dopamine were not examined in this study, since it had been replicated in previous studies. Percent change in HSP70 also showed differences among the groups. Post-hot analyses showed that HSP70 responsiveness in the BB group was significantly higher than the control group (p=0.001), which the CB group showed a trend toward being higher than the control group (p=0.06). Furthermore, HSP70 levels positively correlated with inclined screen performance; i.e. latency to fall from the inclined screen increased as the percent change in HSP70 increased (r=0.39, p=0.048)

Authors' Conclusions	There were significant effects of the diets found on several of the measures in this study. The inclined screen, dopamine release and HSP70 results all suggest that there is a range of effectiveness associated with the different berryfruit diets. However, it does not appear that the anthocyanin component is the one solely responsible for these improvements, as the blackcurrant and boysenberry fruits are higher in anthocyanin level, but not as effective in improving motor performance. Future studies should examine other components, such as the proanthocyanidins and flavans,, in addition to the anthocyanins.
Quality	B
Limitations / Comments	Sample size was not reported.

Berry Evidence Tables – Human Studies

Author, Year: Golbe, 1988	**Ref ID**: 15294	**Berries /Constituents**: Blueberries and strawberries
Objective: To examine the hypothesis that Parkinson's disease may be cased by an amino acid chemically related to L-β-methyl-amino-alanine present in 1 or more fruits and vegetables common in the Western diet.		

Study characteristics		**Population**		**Controls**	**Inclusion criteria**	**Exclusion criteria**	**Definitions**
Study design	Case-control study	Age:	62.3±9.2	62.0±9.8	Cases:	Cases-control pairs:	AD:
	Comparative	%Male:	59.3	59.3	PD patients	Either member was not married before age 40 years or was demented.	PD: A diagnosis of idiopathic PD was confirmed by a neurologist specializing in movement disorders
	Retrospective	Race:	ND	ND			
Country:	US	Other:			Controls:		VascDz:
Setting:	Outpatients				Same-sex siblings of the cases who were nearest in age and willing and able to cooperate		Other:
Funding:	ND						
Comments:							

Predictor(s):		Outcome(s):			**Total**	**Population of interest**	**Control**
				N enrolled:	162	81	81
More or less likely to consume a food (a list of fruits & vegetables)	P>Sib if P>Sp and Sib<SibSp; P>Sp and SibN; P=Sp and Sib<SibSp; or p=Sp and SibN. P<Sib if P<Sp and Sib>SibSp; PN and Sib>SibSp;P<Sp and Sib=SibSp, or PN and Sib=SibSp.	OR of PD in those more likely to eat the food to those less likely to eat the food	Mantel-Haenszel method	N analyzed:	162	81	81
				Drop-outs (%):	N/A		

Comments:	Patients and same-sex siblings, in separate interviews, were each asked whether they or their spouse was more likely to eat each item between the time of marriage and age 40 ages. The spouses of patients and same-sex siblings were also interviewed for their dietary habit as internal standard. A reliability research of the method was conducted before the study in 15 patients with PD and their spouses. An item was discarded when less than 70% the pairs agreed on which member was more likely to eat that food item.

Other predictors/outcomes reported (if applicable):	
Follow-up duration (if applicable):	
Reasons for drop out (if applicable):	
Limitations:	Unusual definition of the consumption levels. Too many potential measurement errors due to the study and survey-method designs. The observations should be due to random errors.
Quality (A/B/C): C	Applicability (1/2/3): 2

Outcome(s):	Results (Text)
OR of PD	There was no significant association between preference for consuming blueberries or strawberries and the risk of Parkinson's disease.

Case-Control Pairs Discordant for Preference (Relative to Spouse) for Various Fruits and Vegetables

	Pt>Sib	Pt<Sib	Odds Ratio	P
Blueberries	13	21	0.62	NS
Strawberries	5	12	0.42	NS

*see "Predictors" for the definitions for Pt>Sib and Pt<Sib

Keys: P>Sp, patient more likely than spouse to eat item; P=Sp, patient as likely as spouse to eat item and both did eat item; P<Sp, patient less likely than spouse to eat item; PN, neither the patient nor spouse ate item. Sib>SibSp, sibling more likely than his or her own spouse to eat item; Sib=SibSp, sibling as likely as spouse to eat item and both did eat item; Sib<SibSp, sibling less likely than spouse to eat item; SibN, neither the sibling nor his or her spouse ate item.

Appendix D. List of Excluded Studies

Abd ElGawad HM, Khalifa AE. Quercetin, coenzyme Q10, and L-canavanine as protective agents against lipid peroxidation and nitric oxide generation in endotoxin-induced shock in rat brain. Pharmacol Res. 2001;43(3):257-63. Non-berry chemical

Abe T, Itokawa Y. Effect of ethanol administration on thiamine metabolism and transketolase activity in rats. Int J Vitam Nutr Res. 1977;47(4):307-14. No outcome of interest

Abe T, Okamoto E, Itokawa Y. Biochemical and histological studies on thiamine-deficient and ethanol-fed rats. J Nutr Sci Vitaminol. 1979;25(5):375-83. No outcome of interest

Adachi K, Izumi M, Osano Y, Miura N, Takatsu S, Terao S, Mitsuma T. Polyamine concentrations in the brain of vitamin B12-deficient rats. Exp Biol Med. 2003;228(9):1069-71. No outcome of interest

Agbayewa MO, Bruce VM, Siemens V. Pyridoxine, ascorbic acid and thiamine in Alzheimer and comparison subjects. Can J Psychiatry. 1992;37(9):661-2. N<50 (Food frequency questionnaire)

AhmadAnnuar A, Tabrizi SJ, Fisher EM. Mouse models as a tool for understanding neurodegenerative diseases. Curr Opin Neurol. 2003 ;16(4):451-8. Review

Aikawa H, Suzuki K, Iwasaki Y. Ultrastructural observation on the thalamic neuronal inclusions in young mice. Acta Neuropathol. 1983;59(4):316-8. B vitamin antagonist

Akaike A, Tamura Y, Sato Y, Yokota T. Protective effects of a vitamin B12 analog, methylcobalamin, against glutamate cytotoxicity in cultured cortical neurons. Eur J Pharmacol. 1993;241(1):1-6. No outcome of interest

Almaas R, Saugstad OD, Pleasure D, Rootwelt T. Neuronal formation of free radicals plays a minor role in hypoxic cell death in human NT2-N neurons. Pediatr Res. 2002;51(2):136-43. Non-berry chemical

Almeida OP, Flicker L, Lautenschlager NT, Leedman P, Vasikaran S, van Bockxmeer FM. Contribution of the MTHFR gene to the causal pathway for depression, anxiety and cognitive impairment in later life. Neurobiol Aging. 2005;26(2):251-7. All normal cognition (correlation study)

Amanpreet S, Naidu PS, Kulkarni SK. Quercetin potentiates L-dopa reversal of drug-induced catalepsy in rats: possible COMT/MAO inhibition. Pharmacology. 2003. Non-berry chemical

Anderson C, Checkoway H, Franklin GM, Beresford S, SmithWeller T, Swanson PD. Dietary factors in Parkinson's disease: the role of food groups and specific foods. Mov Disord. 1999;14(1):21-7. Fruit, not berry

Andersson J, Gustafsson K, Fjellstrom C, Sidenvall B, Nydahl M. Five-day food intake in elderly female outpatients with Parkinson's disease, rheumatoid arthritis or stroke. J Nutr Health Aging. 2005. No comparison group (Food frequency questionnaire)

ArmstrongJames M, Ross DT, Chen F, Ebner FF. The effect of thiamine deficiency on the structure and physiology of the rat forebrain. Metab Brain Dis. 1988;3(2):91-124. No outcome of interest

Bambauer HJ, Ueno S, Umar H, Ueck M. Ultracytochemical localization of Ca++-ATPase activity in pituicytes of the neurohypophysis of the guinea pig. Cell Tissue Res. 1984;237(3):491-7. Non-berry chemical

Barbato M, Rodriguez PJ. Thiamine deficiency in patients admitted to a palliative care unit. Palliat Med. 1994;8(4):320-4. Ineligible population (and/or no sub-analysis of age-related neurocognitive disease)

Beal MF, Henshaw DR, Jenkins BG, Rosen BR, Schulz JB. Coenzyme Q10 and nicotinamide block striatal lesions produced by the mitochondrial toxin malonate. Ann Neurol. 1994;36(6):882-8. Wrong model (mitochondrial defect)

Bell IR, Edman JS, Marby DW, Satlin A, Dreier T, Liptzin B, Cole JO. Vitamin B12 and folate status in acute geropsychiatric inpatients: affective and cognitive characteristics of a vitamin nondeficient population. Biol Psychiatry. 1990;27(2):125-37. N<30 dementia (B12 or Folate correlation)

Bell IR, Edman JS, Miller J, Hebben N, Linn RT, Ray D, Kayne HL. Relationship of normal serum vitamin B12 and folate levels to cognitive test performance in subtypes of geriatric major depression. J Geriatr Psychiatry Neurol. 1990;3(2):98-105. N<100 (B12 or Folate correlation)

Bettendorff L, Hennuy B, De Clerck A, Wins P. Chloride permeability of rat brain membrane vesicles correlates with thiamine triphosphate content. Brain Res. 1994;652(1):157-60. No outcome of interest

Bettendorff L, Hennuy B, Wins P, Schoffeniels E. Thiamin and derivatives as modulators of rat brain chloride channels. Neuroscience. 1993;52(4):1009-17. No outcome of interest

Bettendorff L, Kolb HA, Schoffeniels E. Thiamine triphosphate activates an anion channel of large unit conductance in neuroblastoma cells. J Membr Biol. 1993;136(3):281-8. No outcome of interest

Bettendorff L, Mastrogiacomo F, Wins P, Kish SJ, Grisar T, Ball MJ. Low thiamine diphosphate levels in brains of patients with frontal lobe degeneration of the non-Alzheimer's type. J Neurochem. 1997;69(5):2005-10. Ineligible population (and/or no sub-analysis of age-related neurocognitive disease)

Bettendorff L, Wins P, Schoffeniels E. Regulation of ion uptake in membrane vesicles from rat brain by thiamine compounds. Biochem Biophys Res Commun. 1990;171(3):1137-44. No outcome of interest

Bhagavan HN, Stewart CN. Tissue pyridoxal-5'-phosphate content and avoidance behavior in 2-deoxypyridoxine-treated rats. Int J Vitam Nutr Res. 1974. B vitamin antagonist

Bhattacharya R, Lakshmana Rao PV. Pharmacological interventions of cyanide-induced cytotoxicity and DNA damage in isolated rat thymocytes and their protective efficacy in vivo. Toxicol Lett. 2001;119(1):59-70. Non-berry chemical

Bickford P. Motor learning deficits in aged rats are correlated with loss of cerebellar noradrenergic function. Brain Res. 1993;620(1):133-8. Non-berry

Botez MI, Botez T, Maag U. The Wechsler subtests in mild organic brain damage associated with folate deficiency. Psychol Med. 1984;14(2):431-7. Ineligible population (and/or no sub-analysis of age-related neurocognitive disease)

Bottiglieri T, Parnetti L, Arning E, Ortiz T, Amici S, Lanari A, Gallai V. Plasma total homocysteine levels and the C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene: a study in an Italian population with dementia. Mech Ageing Dev. 2001;122(16):2013-23. N<100 (B12 or Folate correlation)

Brown I. Does diet protect against Parkinson's disease? Part 3 - Fruit, vegetables and grains. Nutr Food Sci. 2004. Review

Bunce D, Kivipelto M, Wahlin A. Apolipoprotein e, B vitamins, and cognitive function in older adults. J Gerontol B Psychol Sci Soc Sci. 2005;60(1):P41-8. All normal cognition (correlation study)

Bunce D, Kivipelto M, Wahlin A. Utilization of cognitive support in episodic free recall as a function of apolipoprotein E and vitamin B12 or folate among adults aged 75 years and older. Neuropsychology. 2004;18(2):362-70. All normal cognition (correlation study)

Buxton PK, Davison W, Hyams DE, Irvine WJ. Vitamin B12 status in mentally disturbed elderly patients. Gerontol Clin. 1969;11(1):22-35. N<100 (B12 or Folate correlation)

Calhau C, Martel F, SoaresdaSilva P, HipolitoReis C, Azevedo I. Regulation of [(3)H]MPP(+) transport by phosphorylation/dephosphorylation pathways in RBE4 cells: role of ecto-alkaline phosphatase. Naunyn-Schmiedebergs Arch Pharmacol. 2002;365(5):349-56. Non-berry chemical

Calingasan NY, Baker H, Sheu KF, Gibson GE. Blood-brain barrier abnormalities in vulnerable brain regions during thiamine deficiency. Exp Neurol. 1995;134(1):64-72. B vitamin antagonist

Calingasan NY, Park LC, Gandy SE, Gibson GE. Disturbances of the blood-brain barrier without expression of amyloid precursor protein- containing neuritic clusters or neuronal loss during late stages of thiamine deficiency in guinea pigs. Dev Neurosci. 1998. B vitamin antagonist

Campbell WA, Iskandar MK, Reed ML, Xia W. Endoproteolysis of presenilin in vitro: inhibition by gamma-secretase inhibitors. Biochemistry. 2002;41(10):3372-9. Not B vitamin study

Cao G, Shukitt-Hale B, Bickford PC, Joseph JA, McEwen J, Prior RL. Hyperoxia-induced changes in antioxidant capacity and the effect of dietary antioxidants. J Appl Physiol. 1999 Jun. Non-berry chemical

Carlson RO, Aschmies SH. Tyrosine kinase activity is essential for interleukin-1 beta--stimulated production of interleukin-6 in U373 human astrocytoma cells. J Neurochem. 1995;65(6):2491-9. Non-berry chemical

Casadesus G, ShukittHale B, Joseph JA. Qualitative versus quantitative caloric intake: are they equivalent paths to successful aging? Neurobiol Aging. 2002;23(5):747-69. Review

Chan DK, Woo J, Ho SC, Pang CP, Law LK, Ng PW, Hung WT, Kwok T, Hui E, Orr K, Leung MF, Kay R. Genetic and environmental risk factors for Parkinson's disease in a Chinese population. J Neurol Neurosurg Psychiatry. 1998;65(5):781-4. Fruit, not berry

Chan P, Cheng JT, Tsai JC, Lien GS, Chen FC, Kao PF, Liu JC, Chen YJ, Hsieh MH. Effect of catechin on the activity and gene expression of superoxide dismutase in cultured rat brain astrocytes. Neurosci Lett. 2002;328(3):281-4. Non-berry chemical

Chen CJ, Raung SL, Liao SL, Chen SY. Inhibition of inducible nitric oxide synthase expression by baicalein in endotoxin/cytokine-stimulated microglia. Biochem Pharmacol. 2004;67(5):957-65. Non-berry chemical

Cho J, Lee HK. Wogonin inhibits ischemic brain injury in a rat model of permanent middle cerebral artery occlusion. Biol Pharm Bull. 2004;27(10):1561-4. Non-berry chemical

Choi E, Chee K, Choi M. The anti- and pro-oxidative effects of orally administered flavonoids in normal rats. Nutr Sci. 2004. Non-berry chemical

Cole MG, Prchal JF. Low serum vitamin B12 in Alzheimer-type dementia. Age Ageing. 1984;13(2):101-5. N<100 (B12 or Folate correlation)

Collins RC, Kirkpatrick JB, McDougal DB. Some regional pathologic and metabolic consequences in mouse brain of pyrithiamine-induced thiamine deficiency. J Neuropathol Exp Neurol. 1970;29(1):57-69. B vitamin antagonist

Commenges D, Scotet V, Renaud S, JacqminGadda H, BarbergerGateau P, Dartigues JF. Intake of flavonoids and risk of dementia. Eur J Epidemiol. 2000;16(4):357-63. Non-berry chemical

Conklin DR, Tan KH, Aschner M. Dimethyl sulfoxide, but not acidosis-induced metallothionein mRNA expression in neonatal rat primary astrocyte cultures is inhibited by the bioflavonoid, quercetin. Brain Res. 1998;794(2):304-8. Non-berry chemical

Conte A, Pellegrini S, Tagliazucchi D. Effect of resveratrol and catechin on PC12 tyrosine kinase activities and their synergistic protection from beta-amyloid toxicity. Drugs Exp Clin Res. 2003;29(5-6):243-55. Non-berry chemical

Conte A, Pellegrini S, Tagliazucchi D. Synergistic protection of PC12 cells from beta-amyloid toxicity by resveratrol and catechin. Brain Res Bull. 2003;62(1):29-38. Non-berry chemical

Cowen MA, Green M, Bertollo DN, Abbott K. A treatment for tardive dyskinesia and some other extrapyramidal symptoms.[see comment]. J Clin Psychopharmacol. 1997;17(3):190-3. Combination B vitamin and other treatments

Cunha UG. An investigation of dementia among elderly outpatients. Acta Psychiatr Scand. 1990;82(3):261-3. No B vitamin results

Cyrino LA, Cardoso RC, Hackl LP, Nicolau M. Effect of quercetin on plasma extravasation in rat CNS and dura mater by ACE and NEP inhibition. Phytother Res. 2002;16(6):545-9. Non-berry chemical

Dajas F, Rivera F, Blasina F, Arredondo F, Echeverry C, Lafon L, Morquio A, Heizen H. Cell culture protection and in vivo neuroprotective capacity of flavonoids. Neurotox Res. 2003;5(6):425-32. Non-berry chemical

Dajas F, RiveraMegret F, Blasina F, Arredondo F, AbinCarriquiry JA, Costa G, Echeverry C, Lafon L, Heizen H, Ferreira M, Morquio A. Neuroprotection by flavonoids. Braz J Med Biol Res. 2003;36(12):1613-20. Review

Davies J, Watkins JC. Facilitatory and direct excitatory effects of folate and folinate on single neurones of cat cerebral cortex. Biochem Pharmacol. 1973;22(13):1667-8. No outcome of interest

Davis CW. Assessment of selective inhibition of rat cerebral cortical calcium-independent and calcium-dependent phosphodiesterases in crude extracts using deoxycyclic AMP and potassium ions. Biochim Biophys Acta. 1984;797(3):354-62. Non-berry chemical

de Luis DA, Fernandez N, Arranz M, Aller R, Izaola O. Total homocysteine and cognitive deterioration in people with type 2 diabetes. Diabetes Res Clin Pract. 2002;55(3):185-90. N<100 (B12 or Folate correlation)

de Rijk MC, Breteler MM, den Breeijen JH, Launer LJ, Grobbee DE, van der Meche FG, Hofman A. Dietary antioxidants and Parkinson disease. The Rotterdam Study. Arch Neurol. 1997;54(6):762-5. Non-berry chemical

De Ruvo C, Amodio R, Algeri S, Martelli N, Intilangelo A, D'Ancona GM, Esposito E. Nutritional antioxidants as antidegenerative agents. Int J Dev Neurosci. 2000;18(4-5):359-66. Non-berry chemical

Dekermendjian K, Kahnberg P, Witt MR, Sterner O, Nielsen M, Liljefors T. Structure-activity relationships and molecular modeling analysis of flavonoids binding to the benzodiazepine site of the rat brain GABA(A) receptor complex. J Med Chem. 1999;42(21):4343-50. Non-berry chemical

Diboune M, Ferard G, Ingenbleek Y, Bourguignat A, Spielmann D, SchepplerRoupert C, Tulasne PA, Calon B, Hasselmann M, Sauder P, Glasser N, Metais P. Soybean oil, blackcurrant seed oil, medium-chain triglycerides, and plasma phospholipid fatty acids of stressed patients. Nutrition. 1993. No outcomes of interest

Dines KC, Cotter MA, Cameron NE. Effectiveness of natural oils as sources of gamma-linolenic acid to correct peripheral nerve conduction velocity abnormalities in diabetic rats: modulation by thromboxane A2 inhibition. Prostaglandins Leukot Essent Fatty Acids. 1996;55(3):159-65. Non-berry

Dufouil C, Alperovitch A, Ducros V, Tzourio C. Homocysteine, white matter hyperintensities, and cognition in healthy elderly people. Ann Neurol. 2003;53(2):214-21. No B vitamin results

Durga J. Folate and age-related disease. Folate and age-related disease. 2005. Thesis

Duvoisin RC, Yahr MD, Cote LD. Pyridoxine reversal of L-dopa effects in Parkinsonism. Trans Am Neurol Assoc. 1969;94:81-4. Pyridoxine and L-Dopa effect

Eastley R, Wilcock GK, Bucks RS. Vitamin B12 deficiency in dementia and cognitive impairment: the effects of treatment on neuropsychological function. Int J Geriatr Psychiatry. 2000;15(3):226-33. Retrospective intervention

Ebly EM, Schaefer JP, Campbell NR, Hogan DB. Folate status, vascular disease and cognition in elderly Canadians. Age Ageing. 1998;27(4):485-91. Ineligible population (and/or no sub-analysis of age-related neurocognitive disease)

Elliott P, HooverPlow J. Excess dietary vitamin B6 alters water maze performance in two strains of mice. Nutr Res. 1989. Model of genetic B6 disorder

End DW, Look RA, Shaffer NL, Balles EA, Persico FJ. Non-selective inhibition of mammalian protein kinases by flavinoids in vitro. Res Commun Chem Pathol Pharmacol. 1987;56(1):75-86. Non-berry chemical

Engelhart MJ, Geerlings MI, Ruitenberg A, van Swieten JC, Hofman A, Witteman JC, Breteler MM. Dietary intake of antioxidants and risk of Alzheimer disease. JAMA. 2002;287(24):3223-9. Non-berry chemical

EssamaTjani JC, Guilland JC, Potier dC, Fuchs F, Richard D. Folate status worsens in recently institutionalized elderly people without evidence of functional deterioration. J Am Coll Nutr. 2000. No B vitamin results

Fahn S. 'On-off' phenomenon with levodopa therapy in Parkinsonism. Clinical and pharmacologic correlations and the effect of intramuscular pyridoxine. Neurology. 1974;24(5):431-41. Pyridoxine and L-Dopa effect

Farina E, Pomati S, Mariani C. Observations on dementias with possibly reversible symptoms. Aging Clin Exp Res. 1999;11(5):323-8. No B vitamin results

Feng R, He W, Ochi H. A new murine oxidative stress model associated with senescence. Mech Ageing Dev. 2001;122(6):547-59. Non-berry chemical

Ferriola PC, Cody V, Middleton E Jr. Protein kinase C inhibition by plant flavonoids. Kinetic mechanisms and structure-activity relationships. Biochem Pharmacol. 1989;38(10):1617-24. Non-berry chemical

Fischer P, Gotz ME, Ellinger B, Streifler M, Riederer P, Danielczyk W. Platelet monoamine oxidase B activity and vitamin B12 in dementia. Biol Psychiatry. 1994;35(10):772-4. N<100 (B12 or Folate correlation)

Flicker L, Martins RN, Thomas J, Acres J, Taddei K, Norman P, Jamrozik K, Almeida OP. Homocysteine, Alzheimer genes and proteins, and measures of cognition and depression in older men. J Alzheimers Dis. 2004;6(3):329-36. No B vitamin results

Forti P, Maioli F, Nesi B, Vettori C, Flisi E, Dalmonte E, Zanardi V, Lodi L, Macini P, Caldarera M, Ravaglia G. Conselice study: a population based survey of brain aging in a municipality of the Emilia Romagna region: (A.U.S.L. Ravenna), neuropsychological tests and nutritional status. Arch Gerontol Geriatr. 2005. N<100 (B12 or Folate correlation)

Franchi F, Baio G, Bolognesi AG, Bonassi R, Emiliani S, Gobbi G, Luchetti L, Zurla L. Deficient folate nutritional status and cognitive performances: results from a retrospective study in male elderly inpatients in a geriatric department. Arch Gerontol Geriatr. 2005. Ineligible population (and/or no sub-analysis of age-related neurocognitive disease)

Freeman GB, Nielsen PE, Gibson GE. Effect of age on behavioral and enzymatic changes during thiamin deficiency. Neurobiol Aging. 1987;8(5):429-34. B vitamin antagonist

Freemon FR. Evaluation of patients with progressive intellectual deterioration. Arch Neurol. 1976;33(9):658-9. Ineligible population (and/or no sub-analysis of age-related neurocognitive disease)

Gaitonde MK. Decreased turnover of N-acetylaspartate in the brain of thiamine-deficient rats. J Neurochem. 1979;32(5):1603-4. No outcome of interest

Gale JM, Brosemer RW. Effect of pyrithiamine treatment on potassium ion fluxes in rat cortical slices. Biochim Biophys Acta. 1984;773(1):125-31. B vitamin antagonist

Galli RL, ShukittHale B, Youdim KA, Joseph JA. Fruit polyphenolics and brain aging: nutritional interventions targeting age-related neuronal and behavioral deficits. Ann N Y Acad Sci. 2002;959:128-32. Review

Gallucci M, Zanardo A, De Valentin L, Vianello A. Homocysteine in Alzheimer disease and vascular dementia. Arch Gerontol Geriatr Suppl. 2005;(9):195-200. No B vitamin results

Gelinas S, Martinoli MG. Neuroprotective effect of estradiol and phytoestrogens on MPP+-induced cytotoxicity in neuronal PC12 cells. J Neurosci Res. 2002;70(1):90-6. Non-berry chemical

Ghandour H, Chen Z, Selhub J, Rozen R. Mice deficient in methylenetetrahydrofolate reductase exhibit tissue-specific distribution of folates. J Nutr. 2004;134(11):2975-8. No outcome of interest

Gibson G, Nielsen P, Mykytyn V, Carlson K, Blass J. Regionally selective alterations in enzymatic activities and metabolic fluxes during thiamin deficiency. Neurochem Res. 1989;14(1):17-24. No outcome of interest

Gibson GE, Calingasan NY, Baker H, Gandy S, Sheu KF. Importance of vascular changes in selective neurodegeneration with thiamine deficiency. Ann N Y Acad Sci. 1997;826:516-9. Review

Gibson GE, KsiezakReding H, Sheu KF, Mykytyn V, Blass JP. Correlation of enzymatic, metabolic, and behavioral deficits in thiamin deficiency and its reversal. Neurochem Res. 1984;9(6):803-14. B vitamin antagonist

Giem P, Beeson WL, Fraser GE. The incidence of dementia and intake of animal products: preliminary findings from the Adventist Health Study. Neuroepidemiology. 1993;12(1):28-36. Non-berry

Glaso M, Nordbo G, Diep L, Bohmer T. Reduced concentrations of several vitamins in normal weight patients with late-onset dementia of the Alzheimer type without vascular disease. J Nutr Health Aging. 2005;8(5):407-13. N<100 (B12 or Folate correlation)

Gomes-Trolin C, Gottfries CG, Regland B, Oreland L. Influence of vitamin B12 on brain methionine adenosyltransferase activity in senile dementia of the Alzheimer's type. J Neural Transm. 1996;103(7):861-72. No outcome of interest

Gomes-Trolin C, Regland B, Oreland L. Decreased methionine adenosyltransferase activity in erythrocytes of patients with dementia disorders. Eur Neuropsychopharmaco. 1995;5(2):107-14. No outcome of interest

Grabow JD, Linkswiler H. Electroencephalographic and nerve-conduction studies in experimental vitamin B 6 deficiency in adults. Am J Clin Nutr. 1969;22(11):1429-34. Ineligible population (and/or no sub-analysis of age-related neurocognitive disease)

Greer A, McBride DH, Shenkin A. Comparison of the nutritional state of new and long-term patients in a psychogeriatric unit. Br J Psychiatry. 1986;149:738-41. No outcome of interest

Gu ZL, Xiao D, Jin LQ, Fan PS, Qian ZN. Effects of quercetin on Na(+)-K(+)-exchanging ATPase and Ca(2+) Mg(2+)-ATPase in rats. Chung Kuo Yao Li Hsueh Pao. 1994;15(5):414-6. Non-berry chemical

Guilarte TR. Reduced NMDA receptor-ion channel function in the vitamin B-6 restricted neonatal rat brain. Neurosci Lett. 1991;121(1-2):207-10. No outcome of interest

Gupta R, Singh M, Sharma A. Neuroprotective effect of antioxidants on ischaemia and reperfusion-induced cerebral injury. Pharmacol Res. 2003;48(2):209-15. Non-berry chemical

Ha HJ, Kwon YS, Park SM, Shin T, Park JH, Kim HC, Kwon MS, Wie MB. Quercetin attenuates oxygen-glucose deprivation- and excitotoxin-induced neurotoxicity in primary cortical cell cultures. Biol Pharm Bull 26(4):544-6. 2003 Non-berry chemical

Hakim AM. Effect of thiamine deficiency and its reversal on cerebral blood flow in the rat. Observations on the phenomena of hyperperfusion, 'no reflow,' and delayed hypoperfusion. J Cereb Blood Flow Metab. 1986;6(1):79-85. No outcome of interest

Haller J, Weggemans RM, Ferry M, Guigoz Y. Mental health: minimental state examination and geriatric depression score of elderly Europeans in the SENECA study of 1993. Eur J Clin Nutr. 1996. All normal cognition (correlation study)

Halliwell B. Antioxidant activity and other biological effects of flavonoids. International Congress and Symposium Series - Royal Society of Medicine. 2000. Review

Hancock MR, Hullin RP, Aylard PR, King JR, Morgan DB. Nutritional state of elderly women on admission to mental hospital. Br J Psychiatry. 1985;147:404-7. Combination B vitamin and other treatments

Hannum SM. Potential impact of strawberries on human health: a review of the science. Crit Rev Food Sci Nutr. 2004;44(1):1-17. Review

Harata N, Iwasaki Y. Evidence for early blood-brain barrier breakdown in experimental thiamine deficiency in the mouse. Metab Brain Dis. 1995;10(2):159-74. B vitamin antagonist

Hassing L, Wahlin A, Winblad B, Backman L. Further evidence on the effects of vitamin B12 and folate levels on episodic memory functioning: a population-based study of healthy very old adults. Biol Psychiatry. 1999;45(11):1472-80. N<100 (B12 or Folate correlation)

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Appendix E. Peer Reviewers

We gratefully acknowledge the following individuals who reviewed the initial draft of this Report and provided us with constructive feedback. Acknowledgments are made with the explicit statement that this does not constitute endorsement of the report.

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