National Toxicology Program
U.S. Department of Health and Human Services

SUPPLEMENTARY MATERIAL: STUDY SUMMARIES

COGNITION AND VITAMIN B12

IDENTIFYING RESEARCH NEEDS FOR ASSESSING SAFE USE OF HIGH INTAKES OF FOLIC ACID

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Office of Health Assessment and Translation
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
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1. CLARKE, 2014

Full citation: Clarke R, Bennett D, Parish S, Lewington S, Skeaff M, Eussen S, Lewerin C, Stott DJ, Armitage J, Hankey GJ, Lonn E, Spence JD, Galan P, de Groot LC, Halsey J, Dangour AD, Collins R, Grodstein F, Coll BVTT. 2014. Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials with cognitive data on 22,000 individuals. American Journal of Clinical Nutrition 100(2): 657-666.

Funding: Supported by the British Heart Foundation, the UK Medical Research Council, Cancer Research UK, and the UK Food Standards Agency (N05072) and Department of Health. Sources of funding for the individual trials are described in their separate publications. The Clinical Trial Service Unit and Epidemiological Studies Unit, where the B-Vitamin Treatment Trialists' Collaboration Secretariat is located, has a policy of not accepting fees, honoraria, or paid consultancies directly or indirectly from industry. It receives funding from the British Heart Foundation, UK Medical Research Council, and Cancer Research UK.

1.1. B vitamins on cognitive aging

Protocol: B vitamins on cognitive aging	
Literature Search Strategy: Other	**Protocol type:** Meta-analysis
Randomized trials were sought by 2 investigators (R Clarke and DB) who searched electronic databases, including PubMed (www.ncbi.nlm.nih.gov/pubmed) and PsychINFO (www.ebscohost. com/academic/psycinfo), with the use of search terms "cognitive function," "cognitive impairment," "cognitive decline," "memory" and "memory impairment," and "folic acid" or "B-vitamins" or "homocysteine lowering therapy" for reports in the English language (Supplemental Figure 1 under "Supplemental data" in the online issue). Unpublished trials were sought through electronic searches, hand-searching reference lists of relevant reports and discussions with experts in the field.	**Inclusion Criteria:** > 100 participants unselected for cognition-related diseases other than heart attack or stroke/transient ischemic attack (TIA), availability of sufficient data by September 2010, duration of > 3 months, English language, homocysteine-lowering treatment only **Exclusion Criteria:**
Starting date:	**Ending date:** 2010-09-01
Total references from search: 120	**References Included:** 11

Additional Notes:

1.2. Result(s)

1.2.ADomain-composite global cognitive function, change from baseline

Studies (4), Total Subjects (1306)

Exposure	Assessed Outcome	other	95% CI (low, high)	Test of Heterogeneity
B vitamins	Domain-composite global cognitive function		(-0.05, 0.06)	X^2,3 = 13.6, p=0.004

Notes:

1.2.B Domain-composite global cognitive function, per year at 25% reduction in homocysteine

Studies (4), Total Subjects (1306)

Exposure	Assessed Outcome	other	95% CI (low, high)	Test of Heterogeneity
B vitamins	Domain-composite global cognitive function	-0.15	(-0.51, 0.2)	

Notes:

1.2.C Executive function domain, change from baseline

Studies (4), Total Subjects (1324)

Exposure	Assessed Outcome	other	95% CI (low, high)	Test of Heterogeneity
B vitamins	Executive function cognitive-domain	-0.05	(-0.14, 0.03)	X^2,3 = 1.4, p=0.71

Notes:

1.2.D Global cognitive function at 25% reduction in homocysteine

Studies (11), Total Subjects (21737)

Exposure	Assessed Outcome	other	95% CI (low, high)	Test of Heterogeneity
B vitamins	Global cognitive function	0.02	(-0.1, 0.13)	X^2,10 = 14.3, P = 0.2

Notes:

1.2.E Memory domain, change from baseline

Studies (4), Total Subjects (1338)

Exposure	Assessed Outcome	other	95% CI (low, high)	Test of Heterogeneity
B vitamins	Memory cognitive-domain	0.02	(-0.06, 0.1)	X^2,3 = 11.3, p=0.01

Notes:

1.2.F MMSE-type global cognitive function, end of treatment

Studies (7), Total Subjects (20431)

Exposure	Assessed Outcome	other	95% CI (low, high)	Test of Heterogeneity
B vitamins	MMSE-type global cognitive function	-0.01	(-0.03, 0.02)	

Notes:

1.2.G MMSE-type global cognitive function, end of treatment at 25% reduction in homocysteine

Studies (7), Total Subjects (20431)

Exposure	Assessed Outcome	other	95% CI (low, high)	Test of Heterogeneity

Exposure	Assessed Outcome	other	95% CI (low, high)	Test of Heterogeneity
B vitamins	MMSE-type global cognitive function	0.04	(-0.09, 0.16)	

Notes:

1.2.HSpeed domain, change from baseline

Studies (4), Total Subjects (1344)

Exposure	Assessed Outcome	other	95% CI (low, high)	Test of Heterogeneity
B vitamins	Speed cognitive-domain	0.03	(-0.02, 0.08)	X^2,3 = 12.3, p=0.006

Notes:

1.3. Statistical Method(s)

Results: Domain-composite global cognitive function, per year at 25% reduction in homocysteine
Adjustment factors: age
Statistical metric description: Change from baseline in z-score: Because the cognitive tests and populations studied differed, scores from each trial were rescaled, as follows: first the residual SDs of the end-treatment domain-specific scores, the domain composite global cognitive function scores, and the MMSE-type global cognitive function scores were estimated after adjustment for end-treatment age (as a continuous variable by using linear regression analysis); then, the before- and after-treatment scores were each scaled by dividing by the estimated residual SD (Supplemental Table 2 under "Supplemental data" in the online issue). Standard linear models and Pearson correlation coefficients were used to compute all statistics on the z scores. The z score differences per year at a 25% homocysteine reduction were estimated by dividing the study z score difference by the trial equivalent years at a 25% homocysteine reduction. These estimates were then divided by the effect of age on the respective global cognitive function score (domain-composite or MMSE-type) estimated over all trials with that score (to provide equivalent years of cognitive aging).

Results: MMSE-type global cognitive function, end of treatment
Adjustment factors: age
Statistical metric description: Change from baseline in z-score: Because the cognitive tests and populations studied differed, scores from each trial were rescaled, as follows: first the residual SDs of the end-treatment domain-specific scores, the domain composite global cognitive function scores, and the MMSE-type global cognitive function scores were estimated after adjustment for end-treatment age (as a continuous variable by using linear regression analysis); then, the before- and after-treatment scores were each scaled by dividing by the estimated residual SD (Supplemental Table 2 under "Supplemental data" in the online issue). Standard linear models and Pearson correlation coefficients were used to compute all statistics on the z scores. For the main comparisons, end-treatment MMSE-type global cognitive function scores were adjusted for age to remove some between-person variation, whereas this was not relevant to comparisons of changes in z scores in the trials. All comparisons were conducted separately within each trial and the trial-specific estimates subsequently combined by using inversevariance–weighted averaging.

Results: Global cognitive function at 25% reduction in homocysteine; MMSE-type global cognitive function, end of treatment at 25% reduction in homocysteine
Adjustment factors: age
Statistical metric description: Change from baseline in z-score: Because the cognitive tests and populations studied differed, scores from each trial were rescaled, as follows: first the residual SDs of the end-treatment domain-specific scores, the domain composite global cognitive function scores, and the MMSE-type global cognitive function scores were estimated after adjustment for end-treatment age (as a continuous variable by using linear regression analysis); then, the before- and after-treatment scores were each scaled by dividing by the estimated residual SD (Supplemental Table 2 under "Supplemental data" in the online issue). Standard linear models and Pearson correlation coefficients were used to compute all statistics on the z scores. For the main comparisons, end-treatment MMSE-type global cognitive function scores were adjusted for age to remove some between-person variation, whereas this was not relevant to comparisons of changes in z scores in the trials. All comparisons were conducted separately within each trial and the trial-specific estimates subsequently combined by using inverse variance–weighted averaging. The z score differences per year at a 25% homocysteine reduction were estimated by dividing the study z score difference by the trial equivalent years at a 25% homocysteine reduction. These estimates were then divided by the effect of age on the respective global cognitive function score (domain-composite or MMSE-type) estimated over all trials with that score (to provide equivalent years of cognitive aging).

Results: Domain-composite global cognitive function, change from baseline; Executive function domain, change from baseline; Memory domain, change from baseline; Speed domain, change from baseline
Adjustment factors:
Statistical metric description: Change from baseline in z-score: Because the cognitive tests and populations studied differed, scores from each trial were rescaled, as follows: first the residual SDs of the end-treatment domain-specific scores, the domain composite global cognitive function scores, and the MMSE-type global cognitive function scores were estimated after adjustment for end-treatment age (as a continuous variable by using linear regression analysis); then, the before- and after-treatment scores were each scaled by dividing by the estimated residual SD (Supplemental Table 2 under "Supplemental data" in the online issue). Standard linear models and Pearson correlation coefficients were used to compute all statistics on the z scores.

2. MALOUF, 2008

Full citation: Malouf R, Evans JG. 2008. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. Cochrane Database of Systematic Reviews(4).
Funding: Internal sources: Division of Clinical Geratology, Nuffield Department of Clinical Medicine, University of Oxford, UK. • Alzheimer's Society, UK. External sources: National Health Service, Research and Development, UK. • Alzheimer's Society, UK.

2.1. Cognitive outcomes for folic acid with or without vitamin B12 in healthy people

Protocol: Cognitive outcomes for folic acid with or without vitamin B12 in healthy people	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG) was searched on 10October 2007 for all years up to December 2005. This register contains records from the major healthcare databases, The Cochrane Library,MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS, and many ongoing trial databases and other grey literature sources. The following search terms were used: folic, folinic, folate, "vitamin B9", VITAMIN-B9, leucovorin, methyltetrahydrofolate. The Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS were searched separately on 10 October 2007 to identify randomized controlled trials with healthy elderly people for the years 2003 to 2007. The search terms used to identify relevant controlled trials on cognition and dementia for the Group's Specialized Register can be found in the Group's module on The Cochrane Library. These search terms were combined with the following search terms and adapted for each database, where appropriate: folic, folinic, folate, "vitamin B9", VITAMIN-B9, leucovorin, methyltetrahydrofolate.	**Inclusion Criteria:** in healthy elderly people or people with any type of dementia or cognitive impairment outcomes, randomized double-blind controlled trial, supplements of folic acid with or without vitamin B12 were compared to placebo **Exclusion Criteria:**
Starting date:	**Ending date:** 2007-10-10
Total references from search: 98	**References Included:** 8

Additional Notes:

2.2. Result(s)

2.2.AMemory, delayed recall

Studies (2), Total Subjects (145)

Exposure	**Assessed Outcome**	mean change	95**% CI (low, high)**	**Test of Heterogeneity**

Exposure	Assessed Outcome	mean change	95% CI (low, high)	Test of Heterogeneity
Folic acid with or without vitamin B12	Memory, delayed recall	0.23	(-1.34, 1.8)	X2=0.33, (P=0.57) I2=0.0%

Notes: Fixed model, Overall effect P=0.77

2.2.B Memory, immediate recall

Studies (2), Total Subjects (145)

Exposure	Assessed Outcome	mean change	95% CI (low, high)	Test of Heterogeneity
Folic acid with or without vitamin B12	Memory, immediate recall	0.27	(-4.14, 4.67)	X2=0.02, (P=0.90) I2=0.0%

Notes: Fixed model, Overall effect P=0.91

2.2.C Memory, word recognition

Studies (2), Total Subjects (144)

Exposure	Assessed Outcome	mean change	95% CI (low, high)	Test of Heterogeneity
Folic acid with or without vitamin B12	Memory, word recognition	0.46	(-0.81, 1.73)	X2=3.12, (P=0.08) I2=68%

Notes: Fixed model, Overall effect P=0.48

2.2.D Verbal ability

Studies (3), Total Subjects (963)

Exposure	Assessed Outcome	mean change	95% CI (low, high)	Test of Heterogeneity
Folic acid with or without vitamin B12	Memory, immediate recall	-0.06	(-0.18, 0.06)	X2=0.17, (P=0.92) I2=0.0%

Notes: Fixed model, Overall effect P=0.31

2.3. Statistical Method(s)

Results: Memory, delayed recall; Memory, immediate recall; Memory, word recognition; Verbal ability
Adjustment factors:
Statistical metric description: The outcomes measured in clinical trials of dementia and cognitive impairment often arise from ordinal rating scales.Where the rating scales used in the trials have a reasonably large number of categories (more than 10) the data were treated as continuous outcomes arising from a normal distribution. Summary statistics (n,mean and standard deviation)were required for each rating scale at each assessment time for each treatment group in each trial for change from baseline. For cross-over trials only the data from the first treatment period were used. When change from baseline results were not reported, the required summary statistics would be calculated from the baseline and assessment time treatment group means and standard deviations. In this case, zero

correlation between the measurements at baseline and assessment time was assumed. This method overestimates the standard deviation of the change from baseline, but this conservative approach is considered to be preferable for meta-analysis. The meta-analysis requires the combination of data from the trials that may not use the same rating scale to assess an outcome. The measure of the treatment difference for any outcome was the weighted mean difference when the pooled trials use the same rating scale or test, and the standardized mean difference, which was the absolute mean difference divided by the standard deviation when different rating scales or tests had been used. The duration of the trials may vary considerably. If the range was considered too great to combine all trials into one meta-analysis it was divided into smaller time periods and a separate meta-analysis conducted for each period. Some trials might contribute data to more than one time period if multiple assessments were made. For binary outcomes, such as clinical improvement or no clinical improvement, the odds ratio was used to measure treatment effect. A weighted estimate of the typical treatment effect across trials was calculated. Overall estimates of the treatment difference were sought. In all cases the overall estimate from a fixed-effects model was to be presented and a test for heterogeneity using a standard chi-square statistic performed. Where there was evidence of heterogeneity of the treatment effect between trials then either only homogeneous results were to be pooled, or a random-effects model be used (in which case the confidence intervals would be broader than those of a fixed-effects model).

3. AGNEW-BLAIS, 2015

Full citation: Agnew-Blais JC, Wassertheil-Smoller S, Kang JH, Hogan PE, Coker LH, Snetselaar LG, Smoller JW. 2015. Folate, Vitamin B-6, and Vitamin B-12 Intake and Mild Cognitive Impairment and Probable Dementia in the Women's Health Initiative Memory Study. Journal of the Academy of Nutrition and Dietetics 115(2): 231-241.

Funding: The Women's Health Initiative (WHI) program is funded by the National Heart, Lung and Blood Institute; National Institutes of Health, US Department of Health and Human Services, through contracts HHSN268201100046C, HSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. The Women's Health Initiative Study of Cognitive Aging (WHISCA) is funded by National Institute on Aging contract number N01-AG-9-2115 and the Women's Health Initiative Memory Study (WHIMS) by National Heart, Lung and Blood Institute contract number HHSN268200464221C, Administrative Data Base number contract N01-WH-4-4221, National Institute on Aging contract HHSN-271-2011-00004C. J. C. Agnew-Blais was supported by a training grant from National Institute of Mental Health (grant no. NIH T32MH017119) while completing the manuscript.

WOMEN'S HEALTH INITIATIVE MEMORY STUDY (WHIMS)

Age: 50.0-79.0 years	**Study design:** Prospective (**n =** 7030)
Gender: Female **Ethnicities:** Asian, Black or African American, Hispanic/Latino, Native American of Other Pacific Islander, White	**Country:** United States **Region:** **State:**
Inclusion criteria: enrolled in the Women's Health Initiative (WHI) Hormone Trial, Postmenopausal women aged 50 through 79 years	**Exclusion critieria:**

3.1. Exposure: Folate intake

Method	Description	Analysis
questionnaire	122-item, self-administered food frequency questionnaire (FFQ)	validation study of the FFQ against other measures (24-hour dietary recall, 4-day food records) showed correlation of 0.59 for folate intake... Most women in WHIMS (69.9%) had baseline folate intake assessed before mandatory folic acid fortification of grain products in the United States; however, for women whose baseline FFQs were returned postfortification, folate intake was adjusted to account for the changes in folic acid content in foods and the different bioavailability of natural folate vs synthetic folic acid from fortification. Supplemental folic acid, vitamin B-6, and vitamin B-12 intake was assessed from pills brought into the WHI study sites by participants and was computed from combining intake from supplements, supplement mixtures (for example B-complex mixtures), and multivitamins.Total folate intake included intake from diet and supplemental sources. In statistical analyses, total and dietary folate, vitamin B-6, and B-12 intake were adjusted for overall caloric intake using the residuals method

Outcomes

	Outcome	Diagnostic Description
A	Mild Cognitive Impairment-Multivariable adjusted (medical professional or test)	In Phase 1 participants who scored below the Modified MiniMental State Examination (3MSE) cutpoint received an in-depth multiphased evaluation, including a battery of neuropsychologic tests, history and physical, neuropsychiatric evaluation, and rigorous adjudication of MCI and dementia. Participants were first administered the 3MSE at baseline and then at yearly intervals. The 3MSE ranges from 0 to 100, and initial cutpoints for further testing were 72 or lower for participants with <9 years of education, and 76 or lower for participants with 9 years; this cutpoint was later raised to increase sensitivity to a score of 80 or lower for participants with <9 years of education, and 88 or lower for the participants with 9 years.32 In Phase 2, participants who scored below the 3MSE cutpoint received the Modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery,the Primary Care Evaluation of Mental Disorders, and the Geriatric Depression Scale.

	Outcome	Diagnostic Description
		The study participant, as well as a designated informant, answered questions related to the participant's acquired cognitive and behavior changes and functional abilities. In Phase 3, participants were assessed by a WHIMS clinic-based physician, experienced in diagnosis of dementia, who reviewed all materials from Phases 1 and 2 and conducted a face-to-face semistructured neurologic evaluation of the participants neuropsychiatric status and history of vascular disease. The physician then made a determination regarding presence of no dementia, MCI, or probable dementia based on Diagnostic and Statistical Manual of Mental Disorders (fourth edition) criteria. The classification of MCI was based on accepted criteria at WHIMS baseline and defined as poor performance (10th or lower percentile based on CERAD norms) on at least one CERAD test, evidence of functional impairment (but not severe enough to interfere with activities of daily living), and the absence of a diagnosis of another psychiatric or medical disorder (including probable dementia) that could explain the cognitive impairment. Participants considered for a diagnosis of MCI or probable dementia received blood tests and a noncontrast computed tomography brain scan to exclude reversible causes of cognitive decline. Final adjudication and diagnosis of dementia and MCI were conducted by expert raters at the WHIMS clinical coordinating center.
B	Mild Cognitive Impairment-Multivariable adjusted, B-6 and B-12 intake adjusted (medical professional or test)	In Phase 1 participants who scored below the Modified MiniMental State Examination (3MSE) cutpoint received an in-depth multiphased evaluation, including a battery of neuropsychologic tests, history and physical, neuropsychiatric evaluation, and rigorous adjudication of MCI and dementia. Participants were first administered the 3MSE at baseline and then at yearly intervals. The 3MSE ranges from 0 to 100, and initial cutpoints for further testing were 72 or lower for participants with <9 years of education, and 76 or lower for participants with 9 years; this cutpoint was later raised to increase sensitivity to a score of 80 or lower for participants with <9 years of education, and 88 or lower for the participants with 9 years.32 In Phase 2, participants who scored below the 3MSE cutpoint received the Modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery,the Primary Care Evaluation of Mental Disorders, and the Geriatric Depression Scale. The study participant, as well as a designated informant, answered questions related to the participant's acquired cognitive and behavior changes and functional abilities. In Phase 3, participants were assessed by a WHIMS clinic-based physician, experienced in diagnosis of dementia, who reviewed all materials from Phases 1 and 2 and conducted a face-to-face semistructured neurologic evaluation of the participants neuropsychiatric status and history of vascular disease. The physician then made a determination regarding presence of no dementia, MCI, or probable dementia based on Diagnostic and Statistical Manual of Mental Disorders (fourth edition) criteria. The classification of MCI was based on accepted criteria at WHIMS baseline and defined as poor performance (10th or lower percentile based on CERAD norms) on at least one CERAD test, evidence of functional impairment (but not severe enough to

	Outcome	Diagnostic Description
		interfere with activities of daily living), and the absence of a diagnosis of another psychiatric or medical disorder (including probable dementia) that could explain the cognitive impairment. Participants considered for a diagnosis of MCI or probable dementia received blood tests and a noncontrast computed tomography brain scan to exclude reversible causes of cognitive decline. Final adjudication and diagnosis of dementia and MCI were conducted by expert raters at the WHIMS clinical coordinating center.

Results

3.1.A Mild Cognitive Impairment- Multivariable adjusted

Population: Women's Health Initiative Memory Study, USA
Exposure: Folate intake
Outcome: Mild Cognitive Impairment- Multivariable adjusted
Statistical metric: adjusted hazard ratio

Group	N	adjHR 95% CI (low, high)	*p*-value
Quartile 1 (<241.25 ug)	-	1.14 (0.77, 1.69)	
Quartile 2 (241.25 < 449.66 ug)	-	1.7 (1.18, 2.46)	0.01
Quartile 3 (449.66 < 695.67 ug)	-	0.88 (0.57, 1.33)	
Quartile 4 (>/= 695.67 ug)	-	1.0	
< RDA (<400ug)	-	1.5 (1.14, 1.97)	0.01

3.1.B Mild Cognitive Impairment- Multivariable adjusted, B-6 and B-12 intake adjusted

Population: Women's Health Initiative Memory Study, USA
Exposure: Folate intake
Outcome: Mild Cognitive Impairment- Multivariable adjusted, B-6 and B-12 intake adjusted
Statistical metric: adjusted hazard ratio

Group	N	adjHR 95% CI (low, high)	*p*-value
Quartile 1 (<241.25 ug)	-	1.61 (0.91, 2.87)	
Quartile 2 (241.25 < 449.66 ug)	-	2.33 (1.39, 3.89)	0.01
Quartile 3 (449.66 < 695.67 ug)	-	0.99 (0.62, 1.56)	
Quartile 4 (>/= 695.67 ug)	-	1.0	
< RDA (<400ug)	-	1.97 (1.32, 2.94)	0.001

Statistical Method(s)

Endpoints: Mild Cognitive Impairment- Multivariable adjusted
Adjustment factors: age, alcohol intake, arm of study enrollment (ie, dietary modification trial, hormone therapy trial, or calcium and vitamin D supplementation trial) from Women's Health Initiative Hormone Trial, body mass index (BMI), education, estrogen plus progestin use, exercise, general health status at baseline, income, race-ethnicity, smoking
Statistical metric: adjusted hazard ratio
Statistical metric description: Cox proportional hazard models were used to estimate hazard ratios (HRs) and associated 95% CIs in relation to MCI/probable dementia, and noncases were censored at the time of the last administration of the 3MSE. The end point of MCI/probable dementia is presented as a combined end point in primary analyses, but these end points were also examined separately. All

models were stratified by randomization assignment in WHI trials and age, as well as in multivariable models, race (because race was not found to meet the proportional hazards assumption). Tests of linear trend for quartiles of intake for B vitamins were conducted in full multivariable models

Endpoints: Mild Cognitive Impairment- Multivariable adjusted, B-6 and B-12 intake adjusted
Adjustment factors: B12 intake, B6 intake, age, alcohol intake, arm of study enrollment (ie, dietary modification trial, hormone therapy trial, or calcium and vitamin D supplementation trial) from Women's Health Initiative Hormone Trial, body mass index (BMI), education, estrogen plus progestin use, exercise, general health status at baseline, income, race-ethnicity, smoking
Statistical metric: adjusted hazard ratio
Statistical metric description: Cox proportional hazard models were used to estimate hazard ratios (HRs) and associated 95% CIs in relation to MCI/probable dementia, and noncases were censored at the time of the last administration of the 3MSE. The end point of MCI/probable dementia is presented as a combined end point in primary analyses, but these end points were also examined separately. All models were stratified by randomization assignment in WHI trials and age, as well as in multivariable models, race (because race was not found to meet the proportional hazards assumption). Tests of linear trend for quartiles of intake for B vitamins were conducted in full multivariable models

4. BELL, 1990A

Full citation: Bell IR, Edman JS, Marby DW, Satlin A, Dreier T, Liptzin B, Cole JO. 1990a. Vitamin B12 and folate status in acute geropsychiatric inpatients: affective and cognitive characteristics of a vitamin nondeficient population. Biol Psychiatry 27(2): 125-137.

Funding: None reported

ACUTE GEROPSYCHIATRIC INPATIENTS

Age: 74.5 (mean), from 60.0-100.0 years	**Study design:** Retrospective (**n =** 102)
Gender: Male and Female **Ethnicities:** White	**Country:** United States **Region:** **State:** Massachusetts
Inclusion criteria: admission to Geriatric psychiatry service	**Exclusion critieria:**

4.1. Exposure: Combined folate/B12 status

Method	Description	Analysis
Serum assay	B12 in pg/mL; Both measured by Becton Dickinson SimulTRAC-SNB radioassay	normal range for B12: 150-950 pg/mL. normal range for folate: 2-16 ng/mL.

Outcomes

	Outcome	Diagnostic Description
A	Admission Mini-Mental State (AD MMS) (medical professional or test)	As part of an ongoing clinical database, the staff psychiatrist or psychiatric resident in charge of each case administered the 18-item HAMD (Hamilton 1960) and the Folstein Mini-Mental State Examination (MMS) (Folstein et al. 1975) on admissiion and discharge

Results

4.1.A Admission Mini-Mental State (AD MMS)

Population: Acute Geropsychiatric Inpatients
Exposure: Combined folate/B12 status
Outcome: Admission Mini-Mental State (AD MMS)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Combined folate/B12 status	-	-	0.05

Statistical Method(s)

Endpoints: Admission Mini-Mental State (AD MMS)
Adjustment factors:

Statistical metric: correlation
Statistical metric description: Stat analyses performed with SPSS-X 2.2 with criterion of $p<0.05$ for significance; missing values were dropped from individual analyses

4.2. Exposure: Serum folate status

Method	Description	Analysis
serum assay	measured by Becton Dickinson SimulTRAC-SNB radioassay	normal range for folate: 2-16 ng/mL.

Outcomes

	Outcome	Diagnostic Description
A	Admission Mini-Mental State (AD MMS) (medical professional or test)	As part of an ongoing clinical database, the staff psychiatrist or psychiatric resident in charge of each case administered the 18-item HAMD (Hamilton 1960) and the Folstein Mini-Mental State Examination (MMS) (Folstein et al. 1975) on admissiion and discharge.
B	Discharge Mini-Mental State (DC MMS) (medical professional or test)	As part of an ongoing clinical database, the staff psychiatrist or psychiatric resident in charge of each case administered the 18-item HAMD (Hamilton 1960) and the Folstein Mini-Mental State Examination (MMS) (Folstein et al. 1975) on admissiion and discharge

Results

4.2.A Admission Mini-Mental State (AD MMS)

Population: Acute Geropsychiatric Inpatients
Exposure: Serum folate status
Outcome: Admission Mini-Mental State (AD MMS)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum Folate	-	0.16	0.1

4.2.B Discharge Mini-Mental State (DC MMS)

Population: Acute Geropsychiatric Inpatients
Exposure: Serum folate status
Outcome: Discharge Mini-Mental State (DC MMS)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum Folate	-	0.25	0.05

Statistical Method(s)

Endpoints: Discharge Mini-Mental State (DC MMS); Admission Mini-Mental State (AD MMS)
Adjustment factors:
Statistical metric: correlation

Statistical metric description: Stat analyses performed with SPSS-X 2.2 with criterion of $p<0.05$ for significance; missing values were dropped from individual analyses

4.3. Exposure: Serum vitamin B12 status

Method	Description	Analysis
serum assay	B12 in pg/mL; measured by Becton Dickinson SimulTRAC-SNB radioassay	normal range for B12: 150-950 pg/mL.

Outcomes

	Outcome	Diagnostic Description
A	Admission Mini-Mental State (AD MMS) (medical professional or test)	As part of an ongoing clinical database, the staff psychiatrist or psychiatric resident in charge of each case administered the 18-item HAMD (Hamilton 1960) and the Folstein Mini-Mental State Examination (MMS) (Folstein et al. 1975) on admissiion and discharge.
B	Discharge Mini-Mental State (DC MMS) (medical professional or test)	As part of an ongoing clinical database, the staff psychiatrist or psychiatric resident in charge of each case administered the 18-item HAMD (Hamilton 1960) and the Folstein Mini-Mental State Examination (MMS) (Folstein et al. 1975) on admissiion and discharge

Results

4.3.A Admission Mini-Mental State (AD MMS)

Population: Acute Geropsychiatric Inpatients
Exposure: Serum vitamin B12 status
Outcome: Admission Mini-Mental State (AD MMS)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
serum vitamin B12	102	0.08	

4.3.B Discharge Mini-Mental State (DC MMS)

Population: Acute Geropsychiatric Inpatients
Exposure: Serum vitamin B12 status
Outcome: Discharge Mini-Mental State (DC MMS)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
serum vitamin B12	102	0.15	

Statistical Method(s)

Endpoints: Discharge Mini-Mental State (DC MMS); Admission Mini-Mental State (AD MMS)
Adjustment factors:
Statistical metric: correlation

Statistical metric description: Stat analyses performed with SPSS-X 2.2 with criterion of $p<0.05$ for significance; missing values were dropped from individual analyses

5. BELL, 1990B

Full citation: Bell IR, Edman JS, Miller J, Hebben N, Linn RT, Ray D, Kayne HL. 1990b. Relationship of normal serum vitamin B12 and folate levels to cognitive test performance in subtypes of geriatric major depression. J Geriatr Psychiatry Neurol 3(2): 98-105.

Funding: None reported

GERIATRIC INPATIENTS WITH DEMENTIA

Age: 74.5 (mean)	**Study design:** Retrospective (**n =** 60)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** United States **Region:** **State:**
Inclusion criteria: discharge diagnosis of unipolar or bipolar affective disorder without organic mental disorder or of dementia with or without depression, vitamin B12 or folate above lower limits of normal range	**Exclusion critieria:** abnormally low vitamin B12 or folate levels

5.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	serum folate levels determined with 125I folate radioassay kit	n/a

Outcomes

	Outcome	Diagnostic Description
A	Associate learning word pairs immediate (ASSOCLRNI) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
B	Associate learning words pairs delayed (ASSOCLRND) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal,

	Outcome	Diagnostic Description
		Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
C	ASSOCLRN%=TRIAL 3 ASSOCLRND/TRIAL 3 ASSOCLRNI (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
D	Boston Naming Test (BNT) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
E	Controlled Oral Word Assocation (FAS) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
F	Delayed Verbal Memory (MEMD) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery

	Outcome	Diagnostic Description
		included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
G	Immediate Verbal Memory (MEMI) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
H	MEM%=MEMD/MEMI (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
I	Mental Control Task (MCT) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
J	VISREP%=VISREPD/VISREPI (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of

	Outcome	Diagnostic Description
		focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
K	Visual reproduction delayed (VISREPD) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
L	Visual reproduction immediate (VISREPI) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).

Results

5.1.A Associate learning word pairs immediate (ASSOCLRNI)

Population: Geriatric Inpatients with Dementia
Exposure: Serum folate
Outcome: Associate learning word pairs immediate (ASSOCLRNI)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-0.14	

5.1.B Associate learning words pairs delayed (ASSOCLRND)

Population: Geriatric Inpatients with Dementia
Exposure: Serum folate

Outcome: Associate learning words pairs delayed (ASSOCLRND)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-0.12	

5.1.C ASSOCLRN%=TRIAL 3 ASSOCLRND/TRIAL 3 ASSOCLRNI

Population: Geriatric Inpatients with Dementia
Exposure: Serum folate
Outcome: ASSOCLRN%=TRIAL 3 ASSOCLRND/TRIAL 3 ASSOCLRNI
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-	

5.1.D Boston Naming Test (BNT)

Population: Geriatric Inpatients with Dementia
Exposure: Serum folate
Outcome: Boston Naming Test (BNT)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-0.12	

5.1.E Controlled Oral Word Assocation (FAS)

Population: Geriatric Inpatients with Dementia
Exposure: Serum folate
Outcome: Controlled Oral Word Assocation (FAS)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	0.01	

5.1.F Delayed Verbal Memory (MEMD)

Population: Geriatric Inpatients with Dementia
Exposure: Serum folate
Outcome: Delayed Verbal Memory (MEMD)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-0.3	

5.1.G Immediate Verbal Memory (MEMI)

Population: Geriatric Inpatients with Dementia
Exposure: Serum folate
Outcome: Immediate Verbal Memory (MEMI)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-0.4	

5.1.H MEM%=MEMD/MEMI

Population: Geriatric Inpatients with Dementia
Exposure: Serum folate
Outcome: MEM%=MEMD/MEMI
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-0.01	

5.1.I Mental Control Task (MCT)

Population: Geriatric Inpatients with Dementia
Exposure: Serum folate
Outcome: Mental Control Task (MCT)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-	

5.1.J VISREP%=VISREPD/VISREPI

Population: Geriatric Inpatients with Dementia
Exposure: Serum folate
Outcome: VISREP%=VISREPD/VISREPI
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-0.09	

5.1.K Visual reproduction delayed (VISREPD)

Population: Geriatric Inpatients with Dementia
Exposure: Serum folate
Outcome: Visual reproduction delayed (VISREPD)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	0.03	

5.1.L Visual reproduction immediate (VISREPI)

Population: Geriatric Inpatients with Dementia
Exposure: Serum folate
Outcome: Visual reproduction immediate (VISREPI)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-0.12	

Statistical Method(s)

Endpoints: Visual reproduction delayed (VISREPD); Immediate Verbal Memory (MEMI); VISREP%=VISREPD/VISREPI; MEM%=MEMD/MEMI; Associate learning words pairs delayed (ASSOCLRND); Boston Naming Test (BNT); Delayed Verbal Memory (MEMD); ASSOCLRN%=TRIAL 3 ASSOCLRND/TRIAL 3 ASSOCLRNI; Controlled Oral Word Assocation (FAS); Associate learning word pairs immediate (ASSOCLRNI); Visual reproduction immediate (VISREPI); Mental Control Task (MCT)
Adjustment factors:
Statistical metric: correlation
Statistical metric description: Pearson correlation coefficients between serum vitamin levels and cognitive subtest scores.

5.2. Exposure: Serum vitamin B12

Method	Description	Analysis
serum measurement	serum B12 levels determined with Becton Dickinson Simul-TRAC-SNB vitamin B12 Co (purified intrinsic factor without R binders)	n/a

Outcomes

	Outcome	Diagnostic Description
A	Associate learning word pairs immediate (ASSOCLRNI) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
B	Associate learning words pairs delayed (ASSOCLRND) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
C	ASSOCLRN%=TRIAL 3	The neuropsychologic battery included tests known to be sensitive to

	Outcome	Diagnostic Description
	ASSOCLRND/TRIAL 3 ASSOCLRNI (medical professional or test)	subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
D	Boston Naming Test (BNT) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
E	Controlled Oral Word Assocation (FAS) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
F	Delayed Verbal Memory (MEMD) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).

	Outcome	Diagnostic Description
G	Immediate Verbal Memory (MEMI) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
H	MEM%=MEMD/MEMI (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
I	Mental Control Task (MCT) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
J	VISREP%=VISREPD/VISREPI (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association;

	Outcome	Diagnostic Description
		F,A,S).
K	Visual reproduction delayed (VISREPD) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).
L	Visual reproduction immediate (VISREPI) (medical professional or test)	The neuropsychologic battery included tests known to be sensitive to subtle changes in brain function in a broad range of areas. These tests consisted of several global measures of cognitive functioning as well as several tests related to specific independent domains of cognitive ability with known predictive relationships to a variety of focal cortical lesions.31 Specifically, the neuropsychologic battery included the Wechsler Adult Intelligence Scale (WAIS-R) (i.e., Verbal, Performance, and Full-Scale Intelligence Quotients), Wechsler Memory Scale (WMS) (i.e. Mental Control, immediate and delayed Logical Memory, Visual Reproduction, Associate Learning subtests), Boston Naming Test (BNT), and a word list generation task from three letters of the alphabet (Controlled Oral Word Association; F,A,S).

Results

5.2.A Associate learning word pairs immediate (ASSOCLRNI)

Population: Geriatric Inpatients with Dementia
Exposure: Serum vitamin B12
Outcome: Associate learning word pairs immediate (ASSOCLRNI)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum vitamin B12	-	0.04	

5.2.B Associate learning words pairs delayed (ASSOCLRND)

Population: Geriatric Inpatients with Dementia
Exposure: Serum vitamin B12
Outcome: Associate learning words pairs delayed (ASSOCLRND)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum vitamin B12	-	-0.02	

5.2.C ASSOCLRN%=TRIAL 3 ASSOCLRND/TRIAL 3 ASSOCLRNI

Population: Geriatric Inpatients with Dementia
Exposure: Serum vitamin B12
Outcome: ASSOCLRN%=TRIAL 3 ASSOCLRND/TRIAL 3 ASSOCLRNI
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum vitamin B12	-	-0.33	

5.2.D Boston Naming Test (BNT)

Population: Geriatric Inpatients with Dementia
Exposure: Serum vitamin B12
Outcome: Boston Naming Test (BNT)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum vitamin B12	-	0.27	

5.2.E Controlled Oral Word Assocation (FAS)

Population: Geriatric Inpatients with Dementia
Exposure: Serum vitamin B12
Outcome: Controlled Oral Word Assocation (FAS)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum vitamin B12	-	-0.09	

5.2.F Delayed Verbal Memory (MEMD)

Population: Geriatric Inpatients with Dementia
Exposure: Serum vitamin B12
Outcome: Delayed Verbal Memory (MEMD)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum vitamin B12	-	-0.09	

5.2.G Immediate Verbal Memory (MEMI)

Population: Geriatric Inpatients with Dementia
Exposure: Serum vitamin B12
Outcome: Immediate Verbal Memory (MEMI)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum vitamin B12	-	0.09	

5.2.H MEM%=MEMD/MEMI

Population: Geriatric Inpatients with Dementia
Exposure: Serum vitamin B12

Outcome: MEM%=MEMD/MEMI
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum vitamin B12	-	-0.2	

5.2.I Mental Control Task (MCT)

Population: Geriatric Inpatients with Dementia
Exposure: Serum vitamin B12
Outcome: Mental Control Task (MCT)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum vitamin B12	-	-0.06	

5.2.J VISREP%=VISREPD/VISREPI

Population: Geriatric Inpatients with Dementia
Exposure: Serum vitamin B12
Outcome: VISREP%=VISREPD/VISREPI
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum vitamin B12	-	0.16	

5.2.K Visual reproduction delayed (VISREPD)

Population: Geriatric Inpatients with Dementia
Exposure: Serum vitamin B12
Outcome: Visual reproduction delayed (VISREPD)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum vitamin B12	-	0.19	

5.2.L Visual reproduction immediate (VISREPI)

Population: Geriatric Inpatients with Dementia
Exposure: Serum vitamin B12
Outcome: Visual reproduction immediate (VISREPI)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum vitamin B12	-	-0.18	

Statistical Method(s)

Endpoints: Immediate Verbal Memory (MEMI); Delayed Verbal Memory (MEMD); Mental Control Task (MCT); VISREP%=VISREPD/VISREPI; Visual reproduction delayed (VISREPD); Associate learning words pairs delayed (ASSOCLRND); Visual reproduction immediate (VISREPI); ASSOCLRN%=TRIAL 3 ASSOCLRND/TRIAL 3 ASSOCLRNI; Associate learning word pairs immediate (ASSOCLRNI); Controlled Oral Word Assocation (FAS); MEM%=MEMD/MEMI; Boston Naming Test (BNT)

Adjustment factors:
Statistical metric: correlation
Statistical metric description: Pearson correlation coefficients between serum vitamin levels and cognitive subtest scores.

6. BELL, 1991

Full citation: Bell IR, Edman JS, Morrow FD, Marby DW, Mirages S, Perrone G, Kayne HL, Cole JO. 1991. B complex vitamin patterns in geriatric and young adult inpatients with major depression. J Am Geriatr Soc 39(3): 252-257.

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GERIATRIC AND YOUNG ADULT INPATIENTS

Age: Geriatric age range: 60-84; Young adult age range: 21-40	**Study design:** Cross-sectional (**n =** 36)
Gender: Male and Female **Ethnicities:** Two or More Races	**Country:** United States **Region:** **State:**
Inclusion criteria: diagnosis of depression	**Exclusion critieria:** medications that interfere with riboflavin such as phenothiazine or tricyclic antidepressants

6.1. Exposure: Serum folate status

Method	Description	Analysis
serum assay	folate in ng/mL; Blood samples for... folate and B12 were drawn in tubes with EDTA preservative between 8-9 am after an overnight fast. Competitive protein-binding assays used to measure plasma folate	n/a

Outcomes

	Outcome	Diagnostic Description
A	Mini-Mental State Examination (MMSE) in Geriatric Inpatients (medical professional or test)	All subjects underwent a semi-structured interview to generate scores on the ... Folstein MMSE
B	Mini-Mental State Examination (MMSE) in Young Adult Inpatients (medical professional or test)	All subjects underwent a semi-structured interview to generate scores on the ... Folstein MMSE

Results

6.1.A Mini-Mental State Examination (MMSE) in Geriatric Inpatients

Population: Geriatric and Young Adult Inpatients
Exposure: Serum folate status
Outcome: Mini-Mental State Examination (MMSE) in Geriatric Inpatients
Statistical metric: adjusted coefficient

Group	N	adjusted coefficient 95% CI (low, high)	*p*-value
Serum folate	-	-0.11	

6.1.B Mini-Mental State Examination (MMSE) in Young Adult Inpatients

Population: Geriatric and Young Adult Inpatients
Exposure: Serum folate status
Outcome: Mini-Mental State Examination (MMSE) in Young Adult Inpatients
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	0.22	

Statistical Method(s)

Endpoints: Mini-Mental State Examination (MMSE) in Young Adult Inpatients
Adjustment factors:
Statistical metric: correlation
Statistical metric description: statistical analysis performed with SPSS-PC... including Pearson correlation coefficients

Endpoints: Mini-Mental State Examination (MMSE) in Geriatric Inpatients
Adjustment factors:
Statistical metric: adjusted coefficient
Statistical metric description: statistical analysis performed with SPSS-PC... including Pearson correlation coefficients

6.2. Exposure: Serum vitamin B12 status

Method	Description	Analysis
serum assay	vitamin B12 in pg/mL. Blood samples for... folate and B12 were drawn in tubes with EDTA preservative between 8-9 am after an overnight fast. Competitive protein-binding assays used to measure plasma B12	n/a

Outcomes

	Outcome	Diagnostic Description
A	Mini-Mental State Examination (MMSE) in Geriatric Inpatients (medical professional or test)	All subjects underwent a semi-structured interview to generate scores on the ... Folstein MMSE
B	Mini-Mental State Examination (MMSE) in Young Adult Inpatients (medical professional or test)	All subjects underwent a semi-structured interview to generate scores on the ... Folstein MMSE

Results

6.2.A Mini-Mental State Examination (MMSE) in Geriatric Inpatients

Population: Geriatric and Young Adult Inpatients
Exposure: Serum vitamin B12 status
Outcome: Mini-Mental State Examination (MMSE) in Geriatric Inpatients
Statistical metric: adjusted coefficient

Group	N	adjusted coefficient 95% CI (low, high)	*p*-value
Serum vitamin B12	-	-0.38	

6.2.B Mini-Mental State Examination (MMSE) in Young Adult Inpatients

Population: Geriatric and Young Adult Inpatients
Exposure: Serum vitamin B12 status
Outcome: Mini-Mental State Examination (MMSE) in Young Adult Inpatients
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum vitamin B12	-	-0.12	

Statistical Method(s)

Endpoints: Mini-Mental State Examination (MMSE) in Young Adult Inpatients
Adjustment factors:
Statistical metric: correlation
Statistical metric description: statistical analysis performed with SPSS-PC... including Pearson correlation coefficients

Endpoints: Mini-Mental State Examination (MMSE) in Geriatric Inpatients
Adjustment factors:
Statistical metric: adjusted coefficient
Statistical metric description: statistical analysis performed with SPSS-PC... including Pearson correlation coefficients

7. BRYAN, 2004

Full citation: Bryan J and Calvaresi E. Associations between dietary intake of folate and vitamins B-12 and B-6 and self-reported cognitive function and psychological well-being in Australian men and women in midlife. J Nutr Health Aging 2004; 8 (4):226-32.

Funding: None reported

MIDDLE-AGED AUSTRALIANS

Age: 50.59 (mean), from 39.0-65.0 years	**Study design:** Cross-sectional (**n =** 1217)
Gender: Male and Female **Ethnicities:**	**Country:** Australia **Region:** South Australia **State:**
Inclusion criteria:	**Exclusion critieria:** non-proficient in English

7.1. Exposure: Folate intake

Method	Description	Analysis
questionnaire	Food Frequency Questionnaire based on Baghurst and Record: common 180 food and beverage items consumed per month, week or day	average daiy consumption based in reports of how often specified serving size of each item is consumed+ nutrient composition of food item per unit weight (from food tables)---> daily nutrient intakes to be calculated using FREQUAN dietary analysis program

Outcomes

	Outcome	Diagnostic Description
A	Center for Epidemiological Studies--Depression Scale (CESD) [Depressive Symptoms] (self-reported)	the Center for Epidemiological Studies-- Depression Scale (CESD) is a mood assessment instrument for samples not expected to be clinically depressed. Participants are asked to rate the frequency with which they experience 20 depressive symptoms on a four-point scale ranging from 1(rarely, or none of the time) to 4 (most, or all of the time). Scores range from 20 to 80, with higher scores indicating greater frequency of depressive mood
B	Cognitive Failures (self-reported)	self-report measures (but questionnaire administered...) Cognitive Failures Questionnaire (CFQ): 25 questions about frequency with which participant has made mistakes in perception, memory and motor function during preceding 6 months; responses on a five-point scale from 0(never) to 4 (very often). Scores range from 0 to 100 withhigher scores indicating greater frequency of mistakes
C	Memory Function Questionnaire (MFQ) Frequency of problems (self-reported)	The MFQ contains 64 questions (in 7 sections) to examine the ...frequency and seriousness of common memory problems... on seven-point scales, with higher scores representing better functioning on all domains

	Outcome	Diagnostic Description
D	Memory Function Questionnaire (MFQ) Memory Problems (self-reported)	The MFQ contains 64 questions (in 7 sections) to examine the presence of memory problems, frequency and seriousness of common memory problems... on seven-point scales, with higher scores representing better functioning on all domains
E	Memory Function Questionnaire (MFQ) Poor reading recall (self-reported)	The MFQ contains 64 questions (in 7 sections) to examine the ...quality of recall... on seven-point scales, with higher scores representing better functioning on all domains
F	Memory Function Questionnaire (MFQ) Quality of Recall (self-reported)	The MFQ contains 64 questions (in 7 sections) to examine the presence of memory problems, frequency and seriousness of common memory problems... on seven-point scales, with higher scores representing better functioning on all domains
G	Memory Function Questionnaire (MFQ) Retrospective functioning (self-reported)	The MFQ contains 64 questions (in 7 sections) to examine the presence of memory problems, frequency and seriousness of common memory problems... on seven-point scales, with higher scores representing better functioning on all domains
H	Memory Function Questionnaire (MFQ) Seriousness of Forgetting (self-reported)	The MFQ contains 64 questions (in 7 sections) to examine the presence of memory problems, frequency and seriousness of common memory problems... on seven-point scales, with higher scores representing better functioning on all domains
I	Perceived Stress (self-reported)	Perceived Stress Scale: respond to 14 statements relating to one's thoughts and feelings about events during the last month. Responses rated on five-point scale ranging from 0 (never) to 4 (very often). Scores range from 0 to 56, with higher scores representing higher perceived stress
J	Self Esteem (self-reported)	Bachman revision of Rosenberg Self-Esteem Scale (RSE_B) requires subjects to respond to 10 statements... relating to self-regard, usefulness and competence. The extent to which each statement is true for them is rated on a five-point scale ranging from 1 (almost always true) to 5 (never true). Scores range from 10 to 50, with higher scores indicating higher self-esteem
K	State Anxiety (self-reported)	Spielberger State-Trait Anxiety Inventory, Form Y (STAI-Y) has 2 scales of 20 items each relating to current anxiety state and to usual trait anxiety. Participants required to report the extent to which each statement describes the way they have felt during the past month or with how they usually feel. Responses are rated ona four-point scale ranging from 1(not at all) to 4 (very much so) with higher scores indicating higher state or trait anxiety
L	Trait Anxiety (self-reported)	Spielberger State-Trait Anxiety Inventory, Form Y (STAI-Y) has 2 scales of 20 items each relating to current anxiety state and to usual trait anxiety. Participants required to report the extent to which each statement describes the way they have felt during the past month or with how they usually feel. Responses are rated ona four-point scale ranging from 1(not at all) to 4 (very much so) with higher scores indicating higher state or trait anxiety

Results

7.1.A Center for Epidemiological Studies-- Depression Scale (CESD) [Depressive Symptoms]

Population: Middle-Aged Australian Men and Women
Exposure: Folate intake

Outcome: Center for Epidemiological Studies-- Depression Scale (CESD) [Depressive Symptoms]
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folate intake, men	432	-	
Folate intake, women	751	-	

7.1.B Cognitive Failures

Population: Middle-Aged Australian Men and Women
Exposure: Folate intake
Outcome: Cognitive Failures
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folate intake, men	432	-	
Folate intake, women	751	-	

7.1.C Memory Function Questionnaire (MFQ) Frequency of problems

Population: Middle-Aged Australian Men and Women
Exposure: Folate intake
Outcome: Memory Function Questionnaire (MFQ) Frequency of problems
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folate intake, men	432	-	
Folate intake, women	751	-	

7.1.D Memory Function Questionnaire (MFQ) Memory Problems

Population: Middle-Aged Australian Men and Women
Exposure: Folate intake
Outcome: Memory Function Questionnaire (MFQ) Memory Problems
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folate intake, men	432	-	
Folate intake, women	751	-	

7.1.E Memory Function Questionnaire (MFQ) Poor reading recall

Population: Middle-Aged Australian Men and Women
Exposure: Folate intake
Outcome: Memory Function Questionnaire (MFQ) Poor reading recall
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folate intake, men	432	-	
Folate intake, women	751	-	

7.1.F Memory Function Questionnaire (MFQ) Quality of Recall

Population: Middle-Aged Australian Men and Women
Exposure: Folate intake
Outcome: Memory Function Questionnaire (MFQ) Quality of Recall
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folate intake, men	432	-	
Folate intake, women	751	-	

7.1.G Memory Function Questionnaire (MFQ) Retrospective functioning

Population: Middle-Aged Australian Men and Women
Exposure: Folate intake
Outcome: Memory Function Questionnaire (MFQ) Retrospective functioning
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folate intake, men	432	-	
Folate intake, women	751	-	0.05

7.1.H Memory Function Questionnaire (MFQ) Seriousness of Forgetting

Population: Middle-Aged Australian Men and Women
Exposure: Folate intake
Outcome: Memory Function Questionnaire (MFQ) Seriousness of Forgetting
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folate intake, men	432	-	
Folate intake, women	751	-	

7.1.I Perceived Stress

Population: Middle-Aged Australian Men and Women
Exposure: Folate intake
Outcome: Perceived Stress
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folate intake, men	432	-	
Folate intake, women	751	-	0.05

7.1.J Self Esteem

Population: Middle-Aged Australian Men and Women
Exposure: Folate intake
Outcome: Self Esteem
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folate intake, men	432	-	
Folate intake, women	751	-	

7.1.K State Anxiety

Population: Middle-Aged Australian Men and Women
Exposure: Folate intake
Outcome: State Anxiety
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folate intake, men	432	-	
Folate intake, women	751	-	

7.1.L Trait Anxiety

Population: Middle-Aged Australian Men and Women
Exposure: Folate intake
Outcome: Trait Anxiety
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folate intake, men	432	-	
Folate intake, women	751	-	

Statistical Method(s)

Endpoints: Center for Epidemiological Studies-- Depression Scale (CESD) [Depressive Symptoms]; Perceived Stress; Memory Function Questionnaire (MFQ) Retrospective functioning; Cognitive Failures; Memory Function Questionnaire (MFQ) Memory Problems; Memory Function Questionnaire (MFQ) Frequency of problems; Memory Function Questionnaire (MFQ) Poor reading recall; Memory Function Questionnaire (MFQ) Quality of Recall; Memory Function Questionnaire (MFQ) Seriousness of Forgetting; State Anxiety; Trait Anxiety; Self Esteem
Adjustment factors: age, self-rated health, years of education
Statistical metric: other
Statistical metric description: F-statistic; age, self-rated health and years of education included in model for women only. Values presented as means +/- SD unless stated otherwise... ANOVA and ANCOVA used to assess effects of intake of B-vitamins on self-reported cognitive function and psych. well-being. Post hoc comparisons using Tukey's HSD procedure performed to determine significant differences between intake quartiles, alpha set at 0.05

7.2. Exposure: Vitamin B12 Intake

Method	Description	Analysis
questionnaire	Food Frequency Questionnaire based on Baghurst and Record: common 180 food and beverage items consumed per month, week or day	average daiy consumption based in reports of how often specified serving size of each item is cnsumed+ nutrient composition of food item per unit weight (from food tables)---> daily nutrient intakes to be calculated using FREQUAN dietary analysis program

Outcomes

	Outcome	Diagnostic Description
A	Center for Epidemiological Studies--Depression Scale (CESD) [Depressive Symptoms] (self-reported)	the Center for Epidemiological Studies-- Depression Scale (CESD) is a mood assessment instrument for samples not expected to be clinically depressed. Participants are asked to rate the frequency with which they experience 20 depressive symptoms on a four-point scale ranging from 1(rarely, or none of the time) to 4 (most, or all of the time). Scores range from 20 to 80, with higher scores indicating greater frequency of depressive mood
B	Cognitive Failures (self-reported)	self-report measures (but questionnaire administered...) Cognitive Failures Questionnaire (CFQ): 25 questions about frequency with which participant has made mistakes in perception, memory and motor function during preceding 6 months; responses on a five-point scale from 0(never) to 4 (very often). Scores range from 0 to 100 withhigher scores indicating greater frequency of mistakes
C	Memory Function Questionnaire (MFQ) Frequency of problems (self-reported)	The MFQ contains 64 questions (in 7 sections) to examine the ...frequency and seriousness of common memory problems... on seven-point scales, with higher scores representing better functioning on all domains
D	Memory Function Questionnaire (MFQ) Memory Problems (self-reported)	The MFQ contains 64 questions (in 7 sections) to examine the presence of memory problems, frequency and seriousness of common memory problems... on seven-point scales, with higher scores representing better functioning on all domains
E	Memory Function Questionnaire (MFQ) Poor reading recall (self-reported)	The MFQ contains 64 questions (in 7 sections) to examine the ...quality of recall... on seven-point scales, with higher scores representing better functioning on all domains
F	Memory Function Questionnaire (MFQ) Quality of Recall (self-reported)	The MFQ contains 64 questions (in 7 sections) to examine the presence of memory problems, frequency and seriousness of common memory problems... on seven-point scales, with higher scores representing better functioning on all domains
G	Memory Function Questionnaire (MFQ) Retrospective functioning (self-reported)	The MFQ contains 64 questions (in 7 sections) to examine the presence of memory problems, frequency and seriousness of common memory problems... on seven-point scales, with higher scores representing better functioning on all domains
H	Memory Function Questionnaire (MFQ) Seriousness of Forgetting (self-reported)	The MFQ contains 64 questions (in 7 sections) to examine the presence of memory problems, frequency and seriousness of common memory problems... on seven-point scales, with higher scores representing better functioning on all domains
I	Perceived Stress	Perceived Stress Scale: respond to 14 statements relating to one's

	Outcome	Diagnostic Description
	(self-reported)	thoughts and feelings about events during the last month. Responses rated on five-point scale ranging from 0 (never) to 4 (very often). Scores range from 0 to 56, with higher scores representing higher perceived stress
J	Self Esteem (self-reported)	Bachman revision of Rosenberg Self-Esteem Scale (RSE_B) requires subjects to respond to 10 statements... relating to self-regard, usefulness and competence. The extent to which each statement is true for them is rated on a five-point scale ranging from 1 (almost always true) to 5 (never true). Scores range from 10 to 50, with higher scores indicating higher self-esteem
K	State Anxiety (self-reported)	Spielberger State-Trait Anxiety Inventory, Form Y (STAI-Y) has 2 scales of 20 items each relating to current anxiety state and to usual trait anxiety. Participants required to report the extent to which each statement describes the way they have felt during the past month or with how they usually feel. Responses are rated ona four-point scale ranging from 1(not at all) to 4 (very much so) with higher scores indicating higher state or trait anxiety
L	Trait Anxiety (self-reported)	Spielberger State-Trait Anxiety Inventory, Form Y (STAI-Y) has 2 scales of 20 items each relating to current anxiety state and to usual trait anxiety. Participants required to report the extent to which each statement describes the way they have felt during the past month or with how they usually feel. Responses are rated ona four-point scale ranging from 1(not at all) to 4 (very much so) with higher scores indicating higher state or trait anxiety

Results

7.2.A Center for Epidemiological Studies-- Depression Scale (CESD) [Depressive Symptoms]

Population: Middle-Aged Australian Men and Women
Exposure: Vitamin B12 Intake
Outcome: Center for Epidemiological Studies-- Depression Scale (CESD) [Depressive Symptoms]
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Vitamin B12 intake, men	432	-	
Vitamin B12 intake, women	751	-	

7.2.B Cognitive Failures

Population: Middle-Aged Australian Men and Women
Exposure: Vitamin B12 Intake
Outcome: Cognitive Failures
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Vitamin B12 intake, men	432	-	
Vitamin B12 intake, women	751	-	

7.2.C Memory Function Questionnaire (MFQ) Frequency of problems

Population: Middle-Aged Australian Men and Women
Exposure: Vitamin B12 Intake

Outcome: Memory Function Questionnaire (MFQ) Frequency of problems
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Vitamin B12 intake, men	432	-	
Vitamin B12 intake, women	751	-	

7.2.D Memory Function Questionnaire (MFQ) Memory Problems

Population: Middle-Aged Australian Men and Women
Exposure: Vitamin B12 Intake
Outcome: Memory Function Questionnaire (MFQ) Memory Problems
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Vitamin B12 intake, men	432	-	
Vitamin B12 intake, women	751	-	

7.2.E Memory Function Questionnaire (MFQ) Poor reading recall

Population: Middle-Aged Australian Men and Women
Exposure: Vitamin B12 Intake
Outcome: Memory Function Questionnaire (MFQ) Poor reading recall
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Vitamin B12 intake, men	432	-	
Vitamin B12 intake, women	751	-	

7.2.F Memory Function Questionnaire (MFQ) Quality of Recall

Population: Middle-Aged Australian Men and Women
Exposure: Vitamin B12 Intake
Outcome: Memory Function Questionnaire (MFQ) Quality of Recall
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Vitamin B12 intake, men	432	-	0.05
Vitamin B12 intake, women	751	-	

7.2.G Memory Function Questionnaire (MFQ) Retrospective functioning

Population: Middle-Aged Australian Men and Women
Exposure: Vitamin B12 Intake
Outcome: Memory Function Questionnaire (MFQ) Retrospective functioning
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Vitamin B12 intake, men	432	-	
Vitamin B12 intake, women	751	-	

7.2.H Memory Function Questionnaire (MFQ) Seriousness of Forgetting

Population: Middle-Aged Australian Men and Women
Exposure: Vitamin B12 Intake
Outcome: Memory Function Questionnaire (MFQ) Seriousness of Forgetting
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Vitamin B12 intake, men	432	-	
Vitamin B12 intake, women	751	-	

7.2.I Perceived Stress

Population: Middle-Aged Australian Men and Women
Exposure: Vitamin B12 Intake
Outcome: Perceived Stress
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Vitamin B12 intake, men	432	-	
Vitamin B12 intake, women	751	-	

7.2.J Self Esteem

Population: Middle-Aged Australian Men and Women
Exposure: Vitamin B12 Intake
Outcome: Self Esteem
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Vitamin B12 intake, men	432	-	
Vitamin B12 intake, women	751	-	

7.2.K State Anxiety

Population: Middle-Aged Australian Men and Women
Exposure: Vitamin B12 Intake
Outcome: State Anxiety
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Vitamin B12 intake, men	432	-	
Vitamin B12 intake, women	751	-	

7.2.L Trait Anxiety

Population: Middle-Aged Australian Men and Women
Exposure: Vitamin B12 Intake
Outcome: Trait Anxiety
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Vitamin B12 intake, men	432	-	
Vitamin B12 intake, women	751	-	

Statistical Method(s)

Endpoints: Perceived Stress; Cognitive Failures; Center for Epidemiological Studies-- Depression Scale (CESD) [Depressive Symptoms]; State Anxiety; Trait Anxiety; Memory Function Questionnaire (MFQ) Frequency of problems; Memory Function Questionnaire (MFQ) Poor reading recall; Memory Function Questionnaire (MFQ) Quality of Recall; Memory Function Questionnaire (MFQ) Memory Problems; Memory Function Questionnaire (MFQ) Seriousness of Forgetting; Memory Function Questionnaire (MFQ) Retrospective functioning; Self Esteem
Adjustment factors: age, self-rated health, years of education
Statistical metric: other
Statistical metric description: F-statistic; age, self-rated health and years of education included in model for women only. Values presented as means +/- SD unless stated otherwise... ANOVA and ANCOVA used to assess effects of intake of B-vitamins on self-reported cognitive function and psych. well-being. Post hoc comparisons using Tukey's HSD procedure performed to determine significant differences between intake quartiles, alpha set at 0.05

8. CHENG, 2014

Full citation: Cheng D, Kong H, Pang W, Yang H, Lu H, Huang C, Jiang Y. 2014. B vitamin supplementation improves cognitive function in the middle aged and elderly with hyperhomocysteinemia. Nutr Neurosci.

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B VITAMIN SUPPLEMENTATION AND COGNITIVE FUNCTION

Age: 71.7 (mean)	**Study design:** Controlled trial (**n =** 104)
Gender: Male and Female **Ethnicities:** Asian	**Country:** China **Region:** Tianjin city **State:**
Inclusion criteria: participants with serum tHcy concentration >/= 16 umol/L	**Exclusion critieria:** acoustic or visual disorders, cancer, diabetes, diseases of nervous system, hyper- or hypothyroidism, serious renal or hepatic disease

8.1. Exposure: Supplemental folate, B6, and B12, 14 weeks

Method	Description	Analysis
intervention	daily oral doses of a combination of 800 µg folate, 10 mg vitamin B6, and 25 µg vitamin B12 for 14 weeks	Before and during intervention, subjects were requested to record and keep their regular diet to ensure that the diet did not change throughout the research period.

Outcomes

	Outcome	Diagnostic Description
A	Chinese character comparison (CCC) (medical professional or test)	Basic Cognitive Aptitude Tests (BCATs) were used to evaluate the cognitive function of the subjects. The BCAT includes seven sub-items: digit copy (DC), Chinese character comparison (CCC), mental arithmetic (MA), Chinese character rotation (CCR), recall answer of mental arithmetic (RAMA), recognition of two-word nouns (RTN), and recognition of meaningless figures (RMF), measuring mental speed, reaction capacity, mental efficiency, spatial image ability, digit working memory ability, memory ability on langue [sic] and figure, respectively. The test lasted 10–30 minutes
B	Chinese character rotation (CCR) (medical professional or test)	Basic Cognitive Aptitude Tests (BCATs) were used to evaluate the cognitive function of the subjects. The BCAT includes seven sub-items: digit copy (DC), Chinese character comparison (CCC), mental arithmetic (MA), Chinese character rotation (CCR), recall answer of mental arithmetic (RAMA), recognition of two-word nouns (RTN), and recognition of meaningless figures (RMF), measuring mental speed, reaction capacity, mental efficiency, spatial image ability, digit

	Outcome	Diagnostic Description
		working memory ability, memory ability on langue [sic] and figure, respectively. The test lasted 10–30 minutes
C	Digit copy test (DC) (medical professional or test)	Basic Cognitive Aptitude Tests (BCATs) were used to evaluate the cognitive function of the subjects. The BCAT includes seven sub-items: digit copy (DC), Chinese character comparison (CCC), mental arithmetic (MA), Chinese character rotation (CCR), recall answer of mental arithmetic (RAMA), recognition of two-word nouns (RTN), and recognition of meaningless figures (RMF), measuring mental speed, reaction capacity, mental efficiency, spatial image ability, digit working memory ability, memory ability on langue [sic] and figure, respectively. The test lasted 10–30 minutes
D	Mental arithmetic (MA) (medical professional or test)	Basic Cognitive Aptitude Tests (BCATs) were used to evaluate the cognitive function of the subjects. The BCAT includes seven sub-items: digit copy (DC), Chinese character comparison (CCC), mental arithmetic (MA), Chinese character rotation (CCR), recall answer of mental arithmetic (RAMA), recognition of two-word nouns (RTN), and recognition of meaningless figures (RMF), measuring mental speed, reaction capacity, mental efficiency, spatial image ability, digit working memory ability, memory ability on langue [sic] and figure, respectively. The test lasted 10–30 minutes
E	Recall answer of mental arithmetic (RAMA) (medical professional or test)	Basic Cognitive Aptitude Tests (BCATs) were used to evaluate the cognitive function of the subjects. The BCAT includes seven sub-items: digit copy (DC), Chinese character comparison (CCC), mental arithmetic (MA), Chinese character rotation (CCR), recall answer of mental arithmetic (RAMA), recognition of two-word nouns (RTN), and recognition of meaningless figures (RMF), measuring mental speed, reaction capacity, mental efficiency, spatial image ability, digit working memory ability, memory ability on langue [sic] and figure, respectively. The test lasted 10–30 minutes
F	Recognition of meaningless figures (RMF) (medical professional or test)	Basic Cognitive Aptitude Tests (BCATs) were used to evaluate the cognitive function of the subjects. The BCAT includes seven sub-items: digit copy (DC), Chinese character comparison (CCC), mental arithmetic (MA), Chinese character rotation (CCR), recall answer of mental arithmetic (RAMA), recognition of two-word nouns (RTN), and recognition of meaningless figures (RMF), measuring mental speed, reaction capacity, mental efficiency, spatial image ability, digit working memory ability, memory ability on langue [sic] and figure, respectively. The test lasted 10–30 minutes
G	Recognition of two-word nouns (RTN) (medical professional or test)	Basic Cognitive Aptitude Tests (BCATs) were used to evaluate the cognitive function of the subjects. The BCAT includes seven sub-items: digit copy (DC), Chinese character comparison (CCC), mental arithmetic (MA), Chinese character rotation (CCR), recall answer of mental arithmetic (RAMA), recognition of two-word nouns (RTN), and recognition of meaningless figures (RMF), measuring mental speed, reaction capacity, mental efficiency, spatial image ability, digit working memory ability, memory ability on langue [sic] and figure, respectively. The test lasted 10–30 minutes
H	Total Basic Cognitive Aptitude Test (BCAT) scores (medical professional or test)	Basic Cognitive Aptitude Tests (BCATs) were used to evaluate the cognitive function of the subjects. The BCAT includes seven sub-items: digit copy (DC), Chinese character comparison (CCC), mental arithmetic (MA), Chinese character rotation (CCR), recall answer of

	Outcome	Diagnostic Description
		mental arithmetic (RAMA), recognition of two-word nouns (RTN), and recognition of meaningless figures (RMF), measuring mental speed, reaction capacity, mental efficiency, spatial image ability, digit working memory ability, memory ability on langue [sic] and figure, respectively. The test lasted 10–30 minutes

Results

8.1.A Chinese character comparison (CCC)

Population: B vitamin supplementation and cognitive function, Chinese middle aged elderly
Exposure: Supplemental folate, B6, and B12, 14 weeks
Outcome: Chinese character comparison (CCC)
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Control	41	-	
Intervention group	42	-	

8.1.B Chinese character rotation (CCR)

Population: B vitamin supplementation and cognitive function, Chinese middle aged elderly
Exposure: Supplemental folate, B6, and B12, 14 weeks
Outcome: Chinese character rotation (CCR)
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Control	41	-	
Intervention group	42	-	0.05

8.1.C Digit copy test (DC)

Population: B vitamin supplementation and cognitive function, Chinese middle aged elderly
Exposure: Supplemental folate, B6, and B12, 14 weeks
Outcome: Digit copy test (DC)
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Control	41	-	
Intervention group	42	-	0.05

8.1.D Mental arithmetic (MA)

Population: B vitamin supplementation and cognitive function, Chinese middle aged elderly
Exposure: Supplemental folate, B6, and B12, 14 weeks
Outcome: Mental arithmetic (MA)
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Control	41	-	
Intervention group	42	-	

8.1.E Recall answer of mental arithmetic (RAMA)

Population: B vitamin supplementation and cognitive function, Chinese middle aged elderly
Exposure: Supplemental folate, B6, and B12, 14 weeks
Outcome: Recall answer of mental arithmetic (RAMA)
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Control	41	-	
Intervention group	42	-	0.05

8.1.F Recognition of meaningless figures (RMF)

Population: B vitamin supplementation and cognitive function, Chinese middle aged elderly
Exposure: Supplemental folate, B6, and B12, 14 weeks
Outcome: Recognition of meaningless figures (RMF)
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Control	41	-	
Intervention group	42	-	0.05

8.1.G Recognition of two-word nouns (RTN)

Population: B vitamin supplementation and cognitive function, Chinese middle aged elderly
Exposure: Supplemental folate, B6, and B12, 14 weeks
Outcome: Recognition of two-word nouns (RTN)
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Control	41	-	
Intervention group	42	-	

8.1.H Total Basic Cognitive Aptitude Test (BCAT) scores

Population: B vitamin supplementation and cognitive function, Chinese middle aged elderly
Exposure: Supplemental folate, B6, and B12, 14 weeks
Outcome: Total Basic Cognitive Aptitude Test (BCAT) scores
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Control	41	-	
Intervention group	42	-	0.05

Statistical Method(s)

Endpoints: Digit copy test (DC); Chinese character comparison (CCC); Total Basic Cognitive Aptitude Test (BCAT) scores; Chinese character rotation (CCR); Recall answer of mental arithmetic (RAMA); Recognition of two-word nouns (RTN); Mental arithmetic (MA); Recognition of meaningless figures (RMF)
Adjustment factors:
Statistical metric: t-test

Statistical metric description: All tests were two-tailed and a P value below 0.05 was deemed significant. Comparisons of tHcy, folate, vitamin B6, and vitamin B12 concentrations and cognition scores between the two groups were evaluated with independent samples t-test.

9. CLARKE, 2008

Full citation: Clarke R, Sherliker P, Hin H, Molloy AM, Nexo E, Ueland PM, Emmens K, Scott JM, Evans JG. 2008. Folate and vitamin B12 status in relation to cognitive impairment and anaemia in the setting of voluntary fortification in the UK. Br J Nutr 100(5): 1054-1059.

Funding: The MRC CFAS programme was funded by the Medical Research Council and the Department of Health. The blood collection and analysis was supported by grants from the Medical Research Council, European Union (QLK3-CT-2002-01 775), Health Foundation, London (554/1236), Food Standards Agency, Clothworkers' Foundation and the Joan Dawkins Foundation of the British Medical Association. All the analyses were carried out independently of the sources of support.

OLDER UNITED KINGDOM CITIZENS/RESIDENTS

Age: more than 65	**Study design:** Prospective (**n =** 2741)
Gender: Male and Female **Ethnicities:**	**Country:** United Kingdom **Region:** Oxford City & Oxfordshire **State:**
Inclusion criteria: >65 years of age	**Exclusion critieria:** use of vitamin B12 injections or extreme serum B12 values

9.1. Exposure: Folate status

Method	Description	Analysis
serum assay	Frozen serum samples were thawed for measurements of levels of folate... Serum folate levels were measured using a microbiological method at the University of Dublin, Republic of Ireland for both the OHAP and Banburypopulations	Individuals were defined as having high folate status if serum folate >30 nmol/l for some analyses or >60 nmol/l for other analyses

Outcomes

	Outcome	Diagnostic Description
A	Cognitive impairment (medical professional or test)	Participants also had their cognitive function assessed around the same time as their blood was collected using the Mini-Mental State Examination(12) and cognitive impairment was defined if the Mini-Mental State Examination was <25/30

Results

9.1.A <u>Cognitive impairment</u>

Population: Older United Kingdom citizens/residents
Exposure: Folate status
Outcome: Cognitive impairment
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Folate III (mean: 42.1 nmol/L)	167	1.0 (0.82, 1.22)	
Folate II (mean: 15.5 nmol/L)	190	1.23 (1.04, 1.45)	0.05
Folate I (mean: 7.3 nmol/L)	221	1.55 (1.28, 1.87)	0.05

Statistical Method(s)

Endpoints: Cognitive impairment
Adjustment factors: age, sex, smoking, study (Oxford Healthy Aging Project vs Banbury)
Statistical metric: adjusted odds ratio
Statistical metric description: OR (with 95 % CI) of anaemia and cognitive impairment were estimated using logistic regression after adjustment for age, sex, smoking and study. Since data on some covariates, such as blood pressure, prior CVD and education, were missing on some or all individuals in either population, the primary analyses were adjusted for the covariates with complete data available on all participants. Additional models were carried out in the OHAP population only (that had the relevant data) to also adjust for education

9.2. Exposure: HoloTC (holotranscobalamin) plus Folate status

Method	Description	Analysis
Serum Assay	Frozen serum samples were thawed for measurements of levels of folate, holoTC, B12 and homocysteine (tHcy). Serum holoTC concentrations in the OHAP study were carried out at Aarhus University Hospital, Aarhus, Denmark using an ELISA method modified for use on an automated analyser(13). Serum holoTC levels in the Banbury B12 study were measured at the Oxford University Clinical Trial Service Unit using a RIA (AXIS-Shield ASA, Oslo, Norway)(14) that has been shown to have a very good agreement with the ELISA assay. Serum folate levels were measured using a microbiological method at the University of Dublin, Republic of Ireland for both the OHAP and Banbury populations	Individuals with extreme elevations of vitamin B12 (>1000 pmol/l) or holoTC (>400 pmol/l) were excluded

Outcomes

	Outcome	Diagnostic Description
A	Cognitive impairment (medical professional or test)	cognitive function assessed around the same time as their blood was collected using the Mini-Mental State Examination(12) and cognitive impairment was defined if the Mini-Mental State Examination was <25/30.

Results

9.2.A Cognitive impairment

Population: Older United Kingdom citizens/residents
Exposure: HoloTC (holotranscobalamin) plus Folate status
Outcome: Cognitive impairment
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
HoloTC 45 +, Fol <30	315	1.0 (0.87, 1.15)	
HoloTC 45 +, Fol 30+	67	0.64 (0.49, 0.85)	
HoloTC <45, Fol <30	170	1.45 (1.19, 1.76)	0.05
HoloTC <45, Fol 30+	26	1.5 (0.91, 2.46)	
HoloTC 45 +, Fol <60	362	1.0 (0.88, 1.13)	
HoloTC 45 +, Fol 60+	20	0.87 (0.52, 1.46)	
HoloTC <45, Fol <60	189	1.56 (1.3, 1.88)	0.05
HoloTC <45, Fol 60+	7	2.46 (0.9, 6.71)	

Statistical Method(s)

Endpoints: Cognitive impairment
Adjustment factors: age, sex, smoking, study (Oxford Healthy Aging Project vs Banbury)
Statistical metric: adjusted odds ratio
Statistical metric description: OR (with 95 % CI) of anaemia and cognitive impairment were estimated using logistic regression after adjustment for age, sex, smoking and study. Since data on some covariates, such as blood pressure, prior CVD and education, were missing on some or all individuals in either population, the primary analyses were adjusted for the covariates with complete data available on all participants.

10. DOETS, 2014

Full citation: Doets EL, Ueland PM, Tell GS, Vollset SE, Nygard OK, Van't Veer P, de Groot LC, Nurk E, Refsum H, Smith AD, Eussen SJ. 2014. Interactions between plasma concentrations of folate and markers of vitamin B(12) status with cognitive performance in elderly people not exposed to folic acid fortification: the Hordaland Health Study. Br J Nutr 111(6): 1085-1095.

Funding: The present study was supported by the Norman Collisson Foundation, UK. The laboratory measurements were supported by the Foundation to Promote Research into Functional Vitamin B12 Deficiency, Norway. Both the Norman Collisson Foundation and the Foundation to Promote Research into Functional Vitamin B12 Deficiency had no role in the design, analysis or writing of this article.

NORWEGIAN ELDERLY

Age: 72.5 (mean)	**Study design:** Cross-sectional (**n =** 2203)
Gender: Male and Female **Ethnicities:**	**Country:** Norway **Region:** Bergen **State:**
Inclusion criteria: apparently healthy residents of Bergen (Norway) born between 1925 and 1927, participated both in the Hordaland Homocysteine Study in 1992–3 and in the Hordaland Health Study in 1997–9	**Exclusion critieria:**

10.1. Exposure: Plasma vitamin B12 and folate

Method	Description	Analysis
assay	Plasma concentrations of folate and B12 determined by microbiological assays. A recent study has shown that folate concentrations in plasma are not stable during storage... However, folate determined as p-aminobenzoylglutamate (pABG) equivalents only decreases slowly during storage. We therefore measured pABG equivalents using liquid chromatography–MS/MS in 200 randomly selected samples collected in 1992–3 and 1997–9.	Based on the results of the folate measured as p-aminobenzoylglutamate (pABG) analyses, we corrected for folate degradation during storage by using separate correction factors for the samples collected at baseline (corrected folate concentration 1992–3 =5.3373 + 1.4045 x folate concentration measured in 1992–3) and those collected at follow-up (corrected folate concentration 1997–9 =8.051 + 1.101 x folate concentration measured in 1997–9).

Outcomes

	Outcome	Diagnostic Description
A	Cognitive Impairment (medical professional or test)	Cognitive performance was assessed at the study location by trained nurses and included six tests: a modified version of the Mini-Mental State Examination (m-MMSE; global cognition, maximum score 12); a modified version of the Digit Symbol Test (perceptual speed, score

	Outcome	Diagnostic Description
		reflects the number of digits recalled); a short form of the Block Design (visuospatial skills, maximum score 16); the Kendrick Object Learning Test (episodic memory, maximum score 70); an abridged version of the Controlled Oral Word Association Test (access to semantic memory, score reflects the number of words recalled); the Trail Making Test Part A (executive function, score reflects the number of seconds needed to complete the task). For all tests, a higher score indicates better performance, except for the Trail Making Test Part A where a shorter time used indicates better performance.

Results

10.1.A Cognitive Impairment

Population: Norwegian elderly, Hordaland studies
Exposure: Plasma vitamin B12 and folate
Outcome: Cognitive Impairment
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Normal B12, normal folate	549	1.0	
Normal B12, high folate	273	0.77 (0.43, 1.4)	
Normal B12, low folate	270	0.98 (0.58, 1.66)	
Low B12, normal folate	280	0.94 (0.54, 1.63)	
Low B12, high folate	102	0.22 (0.05, 0.92)	0.05
Low B12, low folate	166	1.01 (0.51, 2.01)	
High B12, normal folate	263	0.84 (0.47, 1.49)	
High B12, high folate	170	0.68 (0.32, 1.44)	
High B12, low folate	113	0.82 (0.38, 1.79)	

Statistical Method(s)

Endpoints: Cognitive Impairment
Adjustment factors: apolipoprotein E-4 (apoE-4), education, history of CVD/hypertension, serum creatinine, sex
Statistical metric: adjusted odds ratio
Statistical metric description: We further studied the interaction by estimating OR for cognitive impairment according to categories of combined folate and vitamin B12 status using logistic regression analyses. Cognitive impairment was defined as the lowest 10th percentile of the combined cognitive performance component as derived from the PCA. We determined quartiles for the markers of folate and vitamin B12 status, and defined the first quartile as 'low', the fourth quartile as 'high' and the two middle quartiles as 'normal'. Categories were created in which we combined 'low', 'normal' or 'high' folate status with 'low', 'normal' or 'high' vitamin B12 status. The combination of normal folate and normal vitamin B12 status was used as the reference group. All analyses were adjusted for sex, education level, history of CVD/hypertension, apoE-14 genotype and creatinine. These covariates were strong predictors for cognitive performance or associated with both B-vitamin levels and cognitive performance, as demonstrated with ANOVA or Pearson's correlation coefficients. BMI, smoking status, consumption of coffee, alcohol use, methylenetetrahydrofolate reductase 677C --> T genotype, diabetes and depression score were associated with either plasma folate or the markers of vitamin B12 or with

cognitive performance, but adjusting for these biological and lifestyle factors did not markedly change the results of the analysis, and are therefore not included in the final model.

11. EUSSEN, 2006

Full citation: Eussen SJ, De Groot LC, Joosten LW, Bloo RJ, Clarke R, Ueland PM, Schneede J, Blom HJ, Hoefnagels WH, Van Staveren WA. 2006. Effect of oral vitamin B-12 with or without folic acid on cognitive function in older people with mild vitamin B-12 deficiency: A randomized, placebo-controlled trial. American Journal of Clinical Nutrition 84(2): 361-370.

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SUPPLEMENTATION WITH B VITAMINS IN DUTCH ELDERLY

Age: 82.0 (mean)	**Study design:** Controlled trial (**n =** 195)
Gender: Male and Female **Ethnicities:**	**Country:** Netherlands **Region:** **State:**
Inclusion criteria: elderly living in care-facility homes, free-living elderly, older than 70 years of age	**Exclusion critieria:** anemia, cobalamin (vitamin B12) supplementation or injections (>50ug/d), diseases of stomach or small intestine, existing dementia, or development of dementia during study, folic acid supplementation or injections (>200ug/d), life-threatening diseases, severe hearing or visual problems, surgery

11.1. Exposure: B-vitamin supplementation

Method	Description	Analysis
supplementation	receive 24 wk of treatment in a parallel group design with daily oral doses of 1) 1000 ug vitamin B-12, 2) a combination of 1000 ug vitamin B-12 and 400 ug folic acid, or 3) a placebo capsule	intervention

Outcomes

	Outcome	Diagnostic Description
A	Excecutive function (medical professional or test)	Cognitive function was assessed by 6 trained and registered neuropsychologists during the run-in period (baseline) and at week 24 of the intervention during a 1.5–2-h session. The MMSE, Clinical Dementia Rating (CDR) Scale, and Geriatric Depression Scale (GDS) were used to describe the study population. Individuals with an MMSE score <19 points (maximum 30 points) were excluded. The CDR classified the study population into participants with no cognitive impairment (CDR = 0), mild cognitive impairment (MCI; CDR = 0.5), moderate cognitive impairment (CDR = 1), or severe cognitive impairment(CDR = 2). The neuropsychologists ascribed a score to the

	Outcome	Diagnostic Description
		CDR according to results of the cognitive test battery and an interview based on the criteria developed by Petersen et al (49). Tests that have been shown to be sensitive to the effects of B vitamin treatment and aging in previous studies were used to measure the potential effects of vitamin B-12 supplementation on cognitive function. Because cognitive status can be influenced by depression, the presence of depression (defined as a score of >=5 out of 15 possible points) was assessed by the GDS. The order of the assessment and a description of the tests, including their corresponding cognitive domain and neuropsychologic focus, are listed in Table 1.
B	Memory (medical professional or test)	Cognitive function was assessed by 6 trained and registered neuropsychologists during the run-in period (baseline) and at week 24 of the intervention during a 1.5–2-h session. The MMSE, Clinical Dementia Rating (CDR) Scale, and Geriatric Depression Scale (GDS) were used to describe the study population. Individuals with an MMSE score <19 points (maximum 30 points) were excluded. The CDR classified the study population into participants with no cognitive impairment (CDR = 0), mild cognitive impairment (MCI; CDR = 0.5), moderate cognitive impairment (CDR = 1), or severe cognitive impairment(CDR = 2). The neuropsychologists ascribed a score to the CDR according to results of the cognitive test battery and an interview based on the criteria developed by Petersen et al (49). Tests that have been shown to be sensitive to the effects of B vitamin treatment and aging in previous studies were used to measure the potential effects of vitamin B-12 supplementation on cognitive function. Because cognitive status can be influenced by depression, the presence of depression (defined as a score of >=5 out of 15 possible points) was assessed by the GDS. The order of the assessment and a description of the tests, including their corresponding cognitive domain and neuropsychologic focus, are listed in Table 1.
C	Sensomotor speed (medical professional or test)	Cognitive function was assessed by 6 trained and registered neuropsychologists during the run-in period (baseline) and at week 24 of the intervention during a 1.5–2-h session. The MMSE, Clinical Dementia Rating (CDR) Scale, and Geriatric Depression Scale (GDS) were used to describe the study population. Individuals with an MMSE score <19 points (maximum 30 points) were excluded. The CDR classified the study population into participants with no cognitive impairment (CDR = 0), mild cognitive impairment (MCI; CDR = 0.5), moderate cognitive impairment (CDR = 1), or severe cognitive impairment(CDR = 2). The neuropsychologists ascribed a score to the CDR according to results of the cognitive test battery and an interview based on the criteria developed by Petersen et al (49). Tests that have been shown to be sensitive to the effects of B vitamin treatment and aging in previous studies were used to measure the potential effects of vitamin B-12 supplementation on cognitive function. Because cognitive status can be influenced by depression, the presence of depression (defined as a score of >=5 out of 15 possible points) was assessed by the GDS. The order of the assessment and a description of the tests, including their

	Outcome	Diagnostic Description
		corresponding cognitive domain and neuropsychologic focus, are listed in Table 1.

Results

11.1.A Excecutive function

Population: B-vitamin supplementation in Dutch elderly
Exposure: B-vitamin supplementation
Outcome: Excecutive function
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Placebo	54	0.1 (0.01, 0.19)	
Vitamin B12 only	51	0.02 (-0.08, 0.12)	
Vitamin B12 +Folic Acid	46	0.07 (-0.05, 0.19)	

11.1.B Memory

Population: B-vitamin supplementation in Dutch elderly
Exposure: B-vitamin supplementation
Outcome: Memory
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Placebo	55	0.39 (0.29, 0.49)	
Vitamin B12 only	53	0.17 (0.04, 0.3)	0.05
Vitamin B12 +Folic Acid	50	0.29 (0.19, 0.39)	0.05

11.1.C Sensomotor speed

Population: B-vitamin supplementation in Dutch elderly
Exposure: B-vitamin supplementation
Outcome: Sensomotor speed
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Placebo	50	0.06 (-0.09, 0.21)	
Vitamin B12 only	47	0.01 (-0.13, 0.15)	
Vitamin B12 +Folic Acid	44	-0.01 (-0.15, 0.13)	

Statistical Method(s)

Endpoints: Memory; Excecutive function; Sensomotor speed
Adjustment factors:
Statistical metric: other
Statistical metric description: The multiple tests for the domains of sensomotor speed, memory, and executive function were clustered to provide compound z scores to reduce the effects of chance findings and to simplify interpretation of the cognitive data...Tukey's post hoc tests were used to compare mean changes in z scores between treatment groups.

12. GÜLTEPE, 2003

Full citation: Gultepe M, Ozcan O, Avsar K, Cetin M, Ozdemir AS, Gok M. 2003. Urine methylmalonic acid measurements for the assessment of cobalamin deficiency related to neuropsychiatric disorders. Clin Biochem 36(4): 275-282.

Funding: None reported

NEUROPSYCHIATRIC PATIENTS WITH DEMENTIA

Age: 41.9 (None)	**Study design:** Cross-sectional (**n =** 108)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Turkey **Region:** **State:**
Inclusion criteria:	**Exclusion critieria:**

12.1. Exposure: B12 and urinary methylmalonic acid (uMMA)

Method	Description	Analysis
serum assay	vitamin B12 measurements were obtained using a microparticle enzymimmunoassay method in Abbott Axsym System Automated Immunoassay Analyzer The urinary MMA measurements were made based on a modified photometric method that utilized a scanning spectrophotometer	Serial dilutions of 20 umol/L MMA standard was used to find the smallest single result can be distinguished from the blank (0.1 N HCl). The standard concentrations of between 0 and 400 umol/L MMA concentrations were analyzed to find linear range of the photometric method

Outcomes

	Outcome	Diagnostic Description
A	Red Cell Folate (medical professional or test)	red cell folate... measurements were obtained using a microparticle enzymimmunoassay method in Abbott Axsym System Automated Immunoassay Analyzer

Results

12.1.A Red Cell Folate

Population: Neuropsychiatric patients
Exposure: B12 and urinary methylmalonic acid (uMMA)
Outcome: Red Cell Folate
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Vit B12	-	0.195	0.006
urinary MMA	-	-6.571	0.001

Statistical Method(s)

Endpoints: Red Cell Folate
Adjustment factors:
Statistical metric: correlation
Statistical metric description: The Pearson correlation coefficients, multiple regression analyses and ROC analysis [11] were used to evaluate the results. The correlation coefficients were accepted when probability was greater than 95% confidence level.

12.2. Exposure: Folate and urinary methylmalonic acid (uMMA)

Method	Description	Analysis
plasma folate & red cell folate assay	folate, red cell folate, ... measurements were obtained using a microparticle enzymimmunoassay method in Abbott Axsym System Automated Immunoassay,Analyzer MMA (umol/L): The urinary MMA measurements were made based on a modified photometric method that utilized a scanning spectrophotometer	The photometric urine MMA determination method is based on the reaction between methylmalonic acid and diazotizated p-nitroaniline. After several trials to optimize the reaction, the method was modified for routine use. Serial dilutions of 20 umol/L MMA standard was used to find the smallest single result can be distinguished from the blank (0.1 N HCl). The standard concentrations of between 0 and 400 umol/L MMA concentrations were analyzed to find linear range of the photometric method.

Outcomes

	Outcome	Diagnostic Description
A	Dementia (medical professional or test)	People between the ages of 58 to 94 yr old admitted to neurology clinic with cognitive symptoms were first tested for dementia. After clinic and laboratory evaluation, the 16 patients were diagnosed with dementia.

Results

12.2.A Dementia

Population: Neuropsychiatric patients
Exposure: Folate and urinary methylmalonic acid (uMMA)
Outcome: Dementia
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
uMMA-p folate	-	0.53	0.01
uMMA-red cell folate	-	-0.67	0.01

Statistical Method(s)

Endpoints: Dementia
Adjustment factors:
Statistical metric: correlation
Statistical metric description: The Pearson correlation coefficients, multiple regression analyses and ROC analysis [11] were used to evaluate the results. The correlation coefficients were accepted when probability was greater than 95% confidence level.

13. HIN, 2006

Full citation: Hin H, Clarke R, Sherliker P, Atoyebi W, Emmens K, Birks J, Schneede J, Ueland PM, Nexo E, Scott J, Molloy A, Donaghy M, Frost C, Evans JG. 2006. Clinical relevance of low serum vitamin B12 concentrations in older people: the Banbury B12 study. Age Ageing 35(4): 416-422.

Funding: This study was supported by a European Union Demonstration Project on the diagnostic utility of holoTC (QLK3-CT-2002-01775) and Health Foundation, London (554/1236). All the analyses were carried out independent of the sources of support.

OLDER RESIDENTS OF BANBURY, ENGLAND

Age: 81.4 (mean)	**Study design:** Cross-sectional (**n =** 1000)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** United Kingdom **Region:** Oxfordshire **State:**
Inclusion criteria: aged 75 years or older living in their own homes, registered with three general practitioners in Banbury, Oxfordshire, England	**Exclusion critieria:** known to have a terminal illness, living in institutions, use of vitamin B12 injections or extreme serum B12 values, vitamin B supplementation

13.1. Exposure: Methylmalonic acid (MMA)

Method	Description	Analysis
MMA mass spectometry	MMA ... measured in the Department of Pharmacology, Bergen, Norway, using stable isotope-dilution capillary gas chromatography–mass spectrometry	The reliability coefficients for the two methods (Bayer assay and Beckman assay) were comparable with each other and with those for...MMA

Outcomes

	Outcome	Diagnostic Description
A	Cognitive impairment, MMSE score <22/30 (medical professional or test)	Cognitive function was assessed using the MiniMental State Examination (MMSE), cognitive impairment being defined as a MMSE score <22/30

Results

13.1.A Cognitive impairment, MMSE score <22/30

Population: Older residents, Banbury
Exposure: Methylmalonic acid (MMA)
Outcome: Cognitive impairment, MMSE score <22/30
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
I quartile (0.18 umol/L, mean)	-	1.0	
II quartile (0.25 umol/L, mean)	-	1.79 (0.6, 3.41)	

Group	N	adjOR 95% CI (low, high)	*p*-value
III quartile (0.32 umol/L, mean)	-	1.43 (0.6, 3.42)	
IV quartile (0.68 umol/L, mean)	-	3.67 (1.68, 8.04)	

Statistical Method(s)

Endpoints: Cognitive impairment, MMSE score <22/30
Adjustment factors: age, sex, smoking
Statistical metric: adjusted odds ratio
Statistical metric description: Logistic regression was used to assess associations of cognitive impairment, depression or neuropathy with quartiles of vitamin status after adjustment for age, sex and smoking

13.2. Exposure: Serum B12

Method	Description	Analysis
Serum assay	Vitamin B12 concentrations were measured at the Horton General Hospital, Banbury, using a Beckman immunoassay that has a reference range of 133–675 pmol/l (180–914 ng/l)	Individuals identified with low vitamin B12 concentrations also had their intrinsic factor antibodies and parietal cell antibodies measured in the Radcliffe Hospital Trust Immunology laboratory.

Outcomes

	Outcome	Diagnostic Description
A	Cognitive impairment, MMSE score <22/30 (medical professional or test)	Cognitive function was assessed using the MiniMental State Examination (MMSE), cognitive impairment being defined as a MMSE score <22/30

Results

13.2.A Cognitive impairment, MMSE score <22/30

Population: Older residents, Banbury
Exposure: Serum B12
Outcome: Cognitive impairment, MMSE score <22/30
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
IV quartile (350 pmol/L, mean)	-	1.0	
III quartile (240 pmol/L, mean)	-	0.99 (0.46, 2.12)	
II quartile (185 pmol/L, mean)	-	1.0 (0.47, 2.12)	
I quartile (125 pmol/L, mean)	-	2.17 (1.11, 4.27)	0.05

Statistical Method(s)

Endpoints: Cognitive impairment, MMSE score <22/30
Adjustment factors: age, sex, smoking
Statistical metric: adjusted odds ratio

Statistical metric description: Logistic regression was used to assess associations of cognitive impairment, depression or neuropathy with quartiles of vitamin status after adjustment for age, sex and smoking

13.3. Exposure: Serum folate

Method	Description	Analysis
Serum assay	Serum folate concentrations were measured using a microbiological assay at the Department of Biochemistry, Trinity College, Dublin, Ireland	n/a

Outcomes

	Outcome	Diagnostic Description
A	Cognitive impairment, MMSE score <22/30 (medical professional or test)	Cognitive function was assessed using the MiniMental State Examination (MMSE), cognitive impairment being defined as a MMSE score <22/30

Results

13.3.A Cognitive impairment, MMSE score <22/30

Population: Older residents, Banbury
Exposure: Serum folate
Outcome: Cognitive impairment, MMSE score <22/30
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
IV quartile (55.3 nmol/L, mean)	-	1.0	
III quartile (27.9 nmol/L, mean)	-	3.31 (1.27, 8.6)	
II quartile (18.6 nmol/L, mean)	-	5.34 (2.14, 13.31)	
I quartile (11.0 nmol/L, mean)	-	3.38 (1.31, 8.7)	

Statistical Method(s)

Endpoints: Cognitive impairment, MMSE score <22/30
Adjustment factors: age, sex, smoking
Statistical metric: adjusted odds ratio
Statistical metric description: Logistic regression was used to assess associations of cognitive impairment, depression or neuropathy with quartiles of vitamin status after adjustment for age, sex and smoking

14. HOOSHMAND, 2012

Full citation: Hooshmand B, Solomon A, Kareholt I, Rusanen M, Hanninen T, Leiviska J, Winblad B, Laatikainen T, Soininen H, Kivipelto M. 2012. Associations between serum homocysteine, holotranscobalamin, folate and cognition in the elderly: a longitudinal study. J Intern Med 271(2): 204-212.

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CARDIOVASCULAR RISK FACTORS, AGING AND DEMENTIA (CAIDE) STUDY

Age: 70.1 (mean), from 65.2-79.9 years	**Study design:** Prospective (**n =** 274)
Gender: Male and Female **Ethnicities:**	**Country:** Finland **Region:** Kuopio; Joensuu **State:**
Inclusion criteria:	**Exclusion critieria:** existing dementia, or development of dementia during study

14.1. Exposure: Serum Folate

Method	Description	Analysis
serum folate assay	serum folate was determined by chemiluminescent microparticle folate binding protein assay using the Architect i system	n/a

Outcomes

	Outcome	Diagnostic Description
A	Episodic Memory (medical professional or test)	used immediate word recall test, a measure of episodic memory;
B	Executive Function (medical professional or test)	the Stroop test, used as a measure of executive functioning
C	Global Cognition (medical professional or test)	The Mini-Mental State Examination
D	Psychomotor Speed (medical professional or test)	the bimanual Purdue Pegboard test and the letter digit substitution test, with the mean of their nnormalized scores used as a measure of psychomotor speed

	Outcome	Diagnostic Description
E	Verbal Expression (medical professional or test)	category fluency test as a measure of verbal expression

Results

14.1.A Episodic Memory

Population: Finnish Seniors of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study
Exposure: Serum Folate
Outcome: Episodic Memory
Statistical metric: adjusted relative difference

Group	N	adjusted relative difference 95% CI (low, high)	*p*-value
Q1 folate (<4.9 nmol/L)	-	1.0 (1.0, 1.0)	
Q2 folate (5.0-6.3 nmol/L)	-	0.92 (0.83, 1.03)	
Q3 folate (6.4-8.4 nmol/L)	-	0.96 (0.87, 1.07)	
Q4 folate (>=8.5 nmol/L)	-	0.92 (0.83, 1.04)	
Folate (continuous)	-	0.96 (0.88, 1.03)	

14.1.B Executive Function

Population: Finnish Seniors of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study
Exposure: Serum Folate
Outcome: Executive Function
Statistical metric: adjusted relative difference

Group	N	adjusted relative difference 95% CI (low, high)	*p*-value
Q1 folate (<4.9 nmol/L)	-	1.0 (1.0, 1.0)	
Q2 folate (5.0-6.3 nmol/L)	-	0.99 (0.89, 1.11)	
Q3 folate (6.4-8.4 nmol/L)	-	1.03 (0.92, 1.14)	
Q4 folate (>=8.5 nmol/L)	-	1.02 (0.91, 1.14)	
Folate (continuous)	-	0.98 (0.91, 1.06)	

14.1.C Global Cognition

Population: Finnish Seniors of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study
Exposure: Serum Folate
Outcome: Global Cognition
Statistical metric: adjusted relative difference

Group	N	adjusted relative difference 95% CI (low, high)	*p*-value
Q1 folate (<4.9 nmol/L)	-	1.0 (1.0, 1.0)	
Q2 folate (5.0-6.3 nmol/L)	-	1.07 (0.98, 1.16)	
Q3 folate (6.4-8.4 nmol/L)	-	1.07 (0.98, 1.16)	
Q4 folate (>=8.5 nmol/L)	-	1.0 (0.92, 1.1)	
Folate (continuous)	-	1.0 (0.94, 1.07)	

14.1.D Psychomotor Speed

Population: Finnish Seniors of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study
Exposure: Serum Folate
Outcome: Psychomotor Speed
Statistical metric: adjusted relative difference

Group	N	adjusted relative difference 95% CI (low, high)	*p*-value
Q1 folate (<4.9 nmol/L)	-	1.0 (1.0, 1.0)	
Q2 folate (5.0-6.3 nmol/L)	-	1.03 (0.92, 1.14)	
Q3 folate (6.4-8.4 nmol/L)	-	1.0 (0.9, 1.12)	
Q4 folate (>=8.5 nmol/L)	-	0.93 (0.83, 1.05)	
Folate (continuous)	-	0.96 (0.89, 1.04)	

14.1.E Verbal Expression

Population: Finnish Seniors of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study
Exposure: Serum Folate
Outcome: Verbal Expression
Statistical metric: adjusted relative difference

Group	N	adjusted relative difference 95% CI (low, high)	*p*-value
Q1 folate (<4.9 nmol/L)	-	1.0 (1.0, 1.0)	
Q2 folate (5.0-6.3 nmol/L)	-	1.04 (0.96, 1.12)	
Q3 folate (6.4-8.4 nmol/L)	-	1.02 (0.95, 1.11)	
Q4 folate (>=8.5 nmol/L)	-	1.03 (0.94, 1.12)	
Folate (continuous)	-	1.01 (0.95, 1.07)	

Statistical Method(s)

Endpoints: Episodic Memory; Executive Function; Global Cognition; Verbal Expression; Psychomotor Speed
Adjustment factors: age, apolipoprotein E-4 (apoE-4), baseline cognitive measures, body mass index (BMI), educational achievement, follow-up time, homocysteine and holotranscobalamin, presence of renal conditions, sex, smoking, stroke, systolic blood pressure (SBP)
Statistical metric: adjusted relative difference
Statistical metric description: Multiple linear regression analyses were performed to investigate the associations between the levels of tHcy, holoTC and folate at the first re-examination (baseline for this study) and cognitive test scores at the second re-examination 7 years later. We analyzed each of the primary predictors as continuous variables and within-quartile categories (with the lowest quartile as the reference category: …</=4.9 nmol/L for folate

15. KANG, 2006

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NURSES' HEALTH STUDY, 1989-2001

Age: 63.0 (mean)	**Study design:** Prospective (**n =** 635)
Gender: Female **Ethnicities:** Unknown/Unspecified	**Country:** United States **Region:** 11 U.S. States **State:**
Inclusion criteria: age 30-55 at enrollement (began in 1976), completed cognitive interview (1995-2001), registered nurse at enrollment	**Exclusion critieria:** did not have folate and vitamin B12 measured, did not provide blood sample (1989-1990), were cases of heart disease, breast cancer, and colon cancer in nested case-control studies

15.1. Exposure: Combined plasma folate and vitamin B12

Method	Description	Analysis
assay	Participants volunteered to send a blood sample by overnight mail, shipped on ice, to our laboratory. Approximately 70% were fasting samples. Ninety-seven percent of the samples were received within 26 hours of being drawn, and the stability of a variety of biomarkers in whole blood for 24 to 48 hours has been previously documented. Samples were processed and separated into plasma, red blood cells, and white blood cells and have been stored in liquid nitrogen freezers. All assays were conducted at the Jean Mayer USDA Human Nutrition Research Center at Tufts University. Levels of folate and vitamin B12 were determined by a radioassay kit (Bio-Rad, Richmond, CA). From each of the 9 batches of different nested case– control studies, blinded replicate samples were included for quality control; the coefficients of variation for folate ranged from 4.8% to 12.0% (median = 9.8%) and for vitamin B12 from 3.6% to 13.7% (median = 8.3%).	The plasma nutrient levels from nonfasting samples were similar but slightly higher than fasting samples; for folate, nonfasting samples were approximately 10% higher on average, and for vitamin B12, levels were approximately 1% higher. Because alternate analyses excluding the nonfasting samples yielded qualitatively similar results, we present analyses presented based on the data from both fasting and nonfasting samples. To evaluate the effect of overall vitamin B status, we examined women with high levels of both folate and vitamin B12 (highest 20th percentile of each nutrient; >14.3 ng/mL for folate and >575.0 pg/mL for vitamin B12) compared with women with low levels of both folate and vitamin B12 (lowest 20th percentile of each nutrient; <5.1 ng/mL for folate and <319.2 pg/mL for vitamin B12).

Outcomes

	Outcome	Diagnostic Description
A	Global score at first interview (medical professional or test)	Global score combines the scores of 6 tests among those with complete data on all tests (TICS, East Boston Immediate recall, East Boston Delayed recall, 10-word list Delayed recall, category fluency, digit span backward); immediate and delayed recalls of the East Boston Memory Test (EBMT; immediate recall: mean = 9, SD = 2, range = 0–12; delayed recall: mean = 9, SD = 2, range = 0–12); a test of category fluency in which women name animals during 1 minute (mean = 17, SD = 5, range = 0–38); a delayed recall of the TICS 10-word list (mean = 2, SD = 2, range = 0–10); and digit span backward, in which women repeat backward increasingly long series of digits (mean = 7, SD = 2, range = 0–12);
B	Telephone Interview for Cognitive Status (TICS) at first interview (medical professional or test)	Telephone Interview for Cognitive Status (TICS; mean score in this population = 34, standard deviation [SD] = 3, range = 8–41); this is a telephone adaptation of the Mini-Mental State Examination.
C	Verbal score at first interview (medical professional or test)	Verbal memory score combines the scores of 4 tests among those with complete data on all tests (10-word list Immediate recall, East

	Outcome	Diagnostic Description
		Boston Immediate recall, East Boston Delayed recall, 10-word list Delayed recall); immediate and delayed recalls of the East Boston Memory Test (EBMT; immediate recall: mean = 9, SD = 2, range = 0–12; delayed recall: mean = 9, SD = 2, range = 0–12); a test of category fluency in which women name animals during 1 minute (mean = 17, SD = 5, range = 0–38); a delayed recall of the TICS 10-word list (mean = 2, SD = 2, range = 0–10);

Results

15.1.A Global score at first interview

Population: Nurses' Health Study, 1989-2001
Exposure: Combined plasma folate and vitamin B12
Outcome: Global score at first interview
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Lowest 20% (<5.1 ng/mL folate and <319.2 pg/mL vitamin B12)	14	-	
Middle	-	0.03 (-0.17, 0.22)	
Highest 20% (>14.3 ng/mL folate and >575.0 pg/mL vitamin B12)	-	0.34 (0.05, 0.62)	

15.1.B Telephone Interview for Cognitive Status (TICS) at first interview

Population: Nurses' Health Study, 1989-2001
Exposure: Combined plasma folate and vitamin B12
Outcome: Telephone Interview for Cognitive Status (TICS) at first interview
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Lowest 20% (<5.1 ng/mL folate and <319.2 pg/mL vitamin B12)	14	-	
Middle	-	-0.13 (-0.86, 0.6)	
Highest 20% (>14.3 ng/mL folate and >575.0 pg/mL vitamin B12)	-	0.71 (-0.28, 1.71)	

15.1.C Verbal score at first interview

Population: Nurses' Health Study, 1989-2001
Exposure: Combined plasma folate and vitamin B12
Outcome: Verbal score at first interview
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Lowest 20% (<5.1 ng/mL folate and <319.2 pg/mL vitamin B12)	14	-	
Middle	-	-0.06 (-0.28, 0.16)	
Highest 20% (>14.3 ng/mL folate and >575.0 pg/mL vitamin B12)	-	0.29 (-0.03, 0.62)	

Statistical Method(s)

Endpoints: Telephone Interview for Cognitive Status (TICS) at first interview; Verbal score at first interview; Global score at first interview
Adjustment factors: age, age at menopause, alcohol intake, antidepressant use, aspirin use, assay batch, body mass index (BMI), education, history of diabetes, history of high blood pressure, history of high cholesterol, mental health index and energy–fatigue index from the Medical Outcomes Short Form-36, physical activity, postmenopausal hormone use, smoking, time between blood draw and cognitive interview, use of vitamin E supplements
Statistical metric: mean change
Statistical metric description: For the main analysis of performance in the initial cognitive interview, we used linear regression to estimate age- and education-adjusted and multivariable-adjusted mean differences in performance across plasma nutrient quartiles. There was little batch-to-batch variation, and the median values for both nutrients were comparable across batches; thus, we analyzed quartiles created from raw values of folate and vitamin B12 to maximize interpretability of results. In an alternate analysis in which we analyzed quartiles created with batch-specific cut points, we confirmed that the results were nearly identical.

15.2. Exposure: Plasma folate

Method	Description	Analysis
assay	Participants volunteered to send a blood sample by overnight mail, shipped on ice, to our laboratory. Approximately 70% were fasting samples. Ninety-seven percent of the samples were received within 26 hours of being drawn, and the stability of a variety of biomarkers in whole blood for 24 to 48 hours has been previously documented. Samples were processed and separated into plasma, red blood cells, and white blood cells and have been stored in liquid nitrogen freezers. All assays were conducted at the Jean Mayer USDA Human Nutrition Research Center at Tufts University. Levels of folate and vitamin B12 were determined by a radioassay kit (Bio-Rad, Richmond, CA). From each of the 9 batches of different nested case– control studies, blinded replicate samples were included for quality control; the coefficients of variation for folate ranged from 4.8% to 12.0% (median = 9.8%) and for vitamin B12 from 3.6% to 13.7% (median = 8.3%).	The plasma nutrient levels from nonfasting samples were similar but slightly higher than fasting samples; for folate, nonfasting samples were approximately 10% higher on average, and for vitamin B12, levels were approximately 1% higher. Because alternate analyses excluding the nonfasting samples yielded qualitatively similar results, we present analyses presented based on the data from both fasting and nonfasting samples.

Outcomes

	Outcome	Diagnostic Description
A	Global score at first interview (medical professional or test)	Global score combines the scores of 6 tests among those with complete data on all tests (TICS, East Boston Immediate recall, East Boston Delayed recall, 10-word list Delayed recall, category fluency, digit span backward); immediate and delayed recalls of the East Boston Memory Test (EBMT; immediate recall: mean = 9, SD = 2, range = 0–12; delayed recall: mean = 9, SD = 2, range = 0–12); a test of category fluency in which women name animals during 1 minute (mean = 17, SD = 5, range = 0–38); a delayed recall of the TICS 10-word list (mean = 2, SD = 2, range = 0–10); and digit span backward, in which women repeat backward increasingly long series of digits (mean = 7, SD = 2, range = 0–12);
B	Global score, Rate of decline over 4 Yr (medical professional or test)	Global score combines the scores of 6 tests among those with complete data on all tests (TICS, East Boston Immediate recall, East Boston Delayed recall, 10-word list Delayed recall, category fluency, digit span backward); immediate and delayed recalls of the East Boston Memory Test (EBMT; immediate recall: mean = 9, SD = 2, range = 0–12; delayed recall: mean = 9, SD = 2, range = 0–12); a test

	Outcome	Diagnostic Description
		of category fluency in which women name animals during 1 minute (mean = 17, SD = 5, range = 0–38); a delayed recall of the TICS 10-word list (mean = 2, SD = 2, range = 0–10); and digit span backward, in which women repeat backward increasingly long series of digits (mean = 7, SD = 2, range = 0–12);
C	Telephone Interview for Cognitive Status (TICS) at first interview (medical professional or test)	Telephone Interview for Cognitive Status (TICS; mean score in this population = 34, standard deviation [SD] = 3, range = 8–41); this is a telephone adaptation of the Mini-Mental State Examination.
D	Telephone Interview for Cognitive Status (TICS), Rate of decline over 4 Yr (medical professional or test)	Telephone Interview for Cognitive Status (TICS; mean score in this population = 34, standard deviation [SD] = 3, range = 8–41); this is a telephone adaptation of the Mini-Mental State Examination.
E	Verbal score at first interview (medical professional or test)	Verbal memory score combines the scores of 4 tests among those with complete data on all tests (10-word list Immediate recall, East Boston Immediate recall, East Boston Delayed recall, 10-word list Delayed recall); immediate and delayed recalls of the East Boston Memory Test (EBMT; immediate recall: mean = 9, SD = 2, range = 0–12; delayed recall: mean = 9, SD = 2, range = 0–12); a test of category fluency in which women name animals during 1 minute (mean = 17, SD = 5, range = 0–38); a delayed recall of the TICS 10-word list (mean = 2, SD = 2, range = 0–10);
F	Verbal score, Rate of decline over 4 Yr (medical professional or test)	Verbal memory score combines the scores of 4 tests among those with complete data on all tests (10-word list Immediate recall, East Boston Immediate recall, East Boston Delayed recall, 10-word list Delayed recall); immediate and delayed recalls of the East Boston Memory Test (EBMT; immediate recall: mean = 9, SD = 2, range = 0–12; delayed recall: mean = 9, SD = 2, range = 0–12); a test of category fluency in which women name animals during 1 minute (mean = 17, SD = 5, range = 0–38); a delayed recall of the TICS 10-word list (mean = 2, SD = 2, range = 0–10);

Results

15.2.A Global score at first interview

Population: Nurses' Health Study, 1989-2001
Exposure: Plasma folate
Outcome: Global score at first interview
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Q1 (4.2 ng/mL)	158	-	
Q2 (6.9 ng/mL)	159	0.13 (-0.02, 0.29)	
Q3 (10.3 ng/mL)	159	0.05 (-0.11, 0.21)	
Q4 (18.7 ng/mL)	159	0.06 (-0.1, 0.22)	

15.2.B Global score, Rate of decline over 4 Yr

Population: Nurses' Health Study, 1989-2001
Exposure: Plasma folate
Outcome: Global score, Rate of decline over 4 Yr
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Q1 (4.2 ng/mL)	158	-	
Q2 (6.9 ng/mL)	159	-0.01 (-0.06, 0.04)	
Q3 (10.3 ng/mL)	159	- (-0.04, 0.05)	
Q4 (18.7 ng/mL)	159	-0.02 (-0.06, 0.03)	

15.2.C Telephone Interview for Cognitive Status (TICS) at first interview

Population: Nurses' Health Study, 1989-2001
Exposure: Plasma folate
Outcome: Telephone Interview for Cognitive Status (TICS) at first interview
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Q1 (4.2 ng/mL)	158	-	
Q2 (6.9 ng/mL)	159	0.22 (-0.32, 0.77)	
Q3 (10.3 ng/mL)	159	-0.03 (-0.58, 0.52)	
Q4 (18.7 ng/mL)	159	-0.06 (-0.61, 0.5)	

15.2.D Telephone Interview for Cognitive Status (TICS), Rate of decline over 4 Yr

Population: Nurses' Health Study, 1989-2001
Exposure: Plasma folate
Outcome: Telephone Interview for Cognitive Status (TICS), Rate of decline over 4 Yr
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Q1 (4.2 ng/mL)	158	-	
Q2 (6.9 ng/mL)	159	0.06 (-0.15, 0.26)	
Q3 (10.3 ng/mL)	159	0.07 (-0.13, 0.28)	
Q4 (18.7 ng/mL)	159	-0.01 (-0.22, 0.19)	

15.2.E Verbal score at first interview

Population: Nurses' Health Study, 1989-2001
Exposure: Plasma folate
Outcome: Verbal score at first interview
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Q1 (4.2 ng/mL)	158	-	
Q2 (6.9 ng/mL)	159	0.12 (-0.06, 0.31)	
Q3 (10.3 ng/mL)	159	0.07 (-0.12, 0.25)	
Q4 (18.7 ng/mL)	159	0.07 (-0.11, 0.26)	

15.2.F Verbal score, Rate of decline over 4 Yr

Population: Nurses' Health Study, 1989-2001
Exposure: Plasma folate
Outcome: Verbal score, Rate of decline over 4 Yr
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Q1 (4.2 ng/mL)	158	-	
Q2 (6.9 ng/mL)	159	- (-0.06, 0.06)	
Q3 (10.3 ng/mL)	159	- (-0.06, 0.06)	
Q4 (18.7 ng/mL)	159	-0.01 (-0.07, 0.05)	

Statistical Method(s)

Endpoints: Telephone Interview for Cognitive Status (TICS) at first interview; Verbal score at first interview; Global score at first interview
Adjustment factors: age, age at menopause, alcohol intake, antidepressant use, aspirin use, assay batch, body mass index (BMI), education, history of diabetes, history of high blood pressure, history of high cholesterol, mental health index and energy–fatigue index from the Medical Outcomes Short Form-36, physical activity, postmenopausal hormone use, smoking, time between blood draw and cognitive interview, use of vitamin E supplements
Statistical metric: mean change
Statistical metric description: For the main analysis of performance in the initial cognitive interview, we used linear regression to estimate age- and education-adjusted and multivariable-adjusted mean differences in performance across plasma nutrient quartiles. There was little batch-to-batch variation, and the median values for both nutrients were comparable across batches; thus, we analyzed quartiles created from raw values of folate and vitamin B12 to maximize interpretability of results. In an alternate analysis in which we analyzed quartiles created with batch-specific cut points, we confirmed that the results were nearly identical.

Endpoints: Telephone Interview for Cognitive Status (TICS), Rate of decline over 4 Yr; Verbal score, Rate of decline over 4 Yr; Global score, Rate of decline over 4 Yr
Adjustment factors: age, age at menopause, alcohol intake, antidepressant use, aspirin use, assay batch, body mass index (BMI), education, history of diabetes, history of high blood pressure, history of high cholesterol, mental health index and energy–fatigue index from the Medical Outcomes Short Form-36, physical activity, postmenopausal hormone use, smoking, time between blood draw and cognitive interview, use of vitamin E supplements
Statistical metric: mean change
Statistical metric description: The estimate of the difference in rate of decline from longitudinal analyses (beta x time x folate and beta x time x vitamin B12). For longitudinal analysis using data from a subset of 391 participants who completed all follow-up interviews to date, we used repeated-measures models incorporating random effects for intercepts and slopes. This approach permits description of individual paths of decline and provides explicit tests regarding the relation of exposures to rates of cognitive change.

15.3. Exposure: Plasma vitamin B12

Method	Description	Analysis
assay	Participants volunteered to send a blood sample by overnight mail, shipped on ice, to our laboratory. Approximately 70% were fasting samples. Ninety-seven percent of the samples were received within 26 hours of being drawn, and the stability of a variety of biomarkers in whole blood for 24 to 48 hours has been previously documented. Samples were processed and separated into plasma, red blood cells, and white blood cells and have been stored in liquid nitrogen freezers. All assays were conducted at the Jean Mayer USDA Human Nutrition Research Center at Tufts University. Levels of folate and vitamin B12 were determined by a radioassay kit (Bio-Rad, Richmond, CA). From each of the 9 batches of different nested case– control studies, blinded replicate samples were included for quality control; the coefficients of variation for folate ranged from 4.8% to 12.0% (median = 9.8%) and for vitamin B12 from 3.6% to 13.7% (median = 8.3%).	The plasma nutrient levels from nonfasting samples were similar but slightly higher than fasting samples; for folate, nonfasting samples were approximately 10% higher on average, and for vitamin B12, levels were approximately 1% higher. Because alternate analyses excluding the nonfasting samples yielded qualitatively similar results, we present analyses presented based on the data from both fasting and nonfasting samples.

Outcomes

	Outcome	Diagnostic Description
A	Global score at first interview (medical professional or test)	Global score combines the scores of 6 tests among those with complete data on all tests (TICS, East Boston Immediate recall, East Boston Delayed recall, 10-word list Delayed recall, category fluency, digit span backward); immediate and delayed recalls of the East Boston Memory Test (EBMT; immediate recall: mean = 9, SD = 2, range = 0–12; delayed recall: mean = 9, SD = 2, range = 0–12); a test of category fluency in which women name animals during 1 minute (mean = 17, SD = 5, range = 0–38); a delayed recall of the TICS 10-word list (mean = 2, SD = 2, range = 0–10); and digit span backward, in which women repeat backward increasingly long series of digits (mean = 7, SD = 2, range = 0–12);
B	Global score, Rate of decline over 4 Yr (medical professional or test)	Global score combines the scores of 6 tests among those with complete data on all tests (TICS, East Boston Immediate recall, East Boston Delayed recall, 10-word list Delayed recall, category fluency, digit span backward); immediate and delayed recalls of the East Boston Memory Test (EBMT; immediate recall: mean = 9, SD = 2, range = 0–12; delayed recall: mean = 9, SD = 2, range = 0–12); a test

	Outcome	Diagnostic Description
		of category fluency in which women name animals during 1 minute (mean = 17, SD = 5, range = 0–38); a delayed recall of the TICS 10-word list (mean = 2, SD = 2, range = 0–10); and digit span backward, in which women repeat backward increasingly long series of digits (mean = 7, SD = 2, range = 0–12);
C	Telephone Interview for Cognitive Status (TICS) at first interview (medical professional or test)	Telephone Interview for Cognitive Status (TICS; mean score in this population = 34, standard deviation [SD] = 3, range = 8–41); this is a telephone adaptation of the Mini-Mental State Examination.
D	Telephone Interview for Cognitive Status (TICS), Rate of decline over 4 Yr (medical professional or test)	Telephone Interview for Cognitive Status (TICS; mean score in this population = 34, standard deviation [SD] = 3, range = 8–41); this is a telephone adaptation of the Mini-Mental State Examination.
E	Verbal score at first interview (medical professional or test)	Verbal memory score combines the scores of 4 tests among those with complete data on all tests (10-word list Immediate recall, East Boston Immediate recall, East Boston Delayed recall, 10-word list Delayed recall); immediate and delayed recalls of the East Boston Memory Test (EBMT; immediate recall: mean = 9, SD = 2, range = 0–12; delayed recall: mean = 9, SD = 2, range = 0–12); a test of category fluency in which women name animals during 1 minute (mean = 17, SD = 5, range = 0–38); a delayed recall of the TICS 10-word list (mean = 2, SD = 2, range = 0–10);
F	Verbal score, Rate of decline over 4 Yr (medical professional or test)	Verbal memory score combines the scores of 4 tests among those with complete data on all tests (10-word list Immediate recall, East Boston Immediate recall, East Boston Delayed recall, 10-word list Delayed recall); immediate and delayed recalls of the East Boston Memory Test (EBMT; immediate recall: mean = 9, SD = 2, range = 0–12; delayed recall: mean = 9, SD = 2, range = 0–12); a test of category fluency in which women name animals during 1 minute (mean = 17, SD = 5, range = 0–38); a delayed recall of the TICS 10-word list (mean = 2, SD = 2, range = 0–10);

Results

15.3.A Global score at first interview

Population: Nurses' Health Study, 1989-2001
Exposure: Plasma vitamin B12
Outcome: Global score at first interview
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Q1 (272 pg/mL)	158	-	
Q2 (385 pg/mL)	159	0.1 (-0.06, 0.25)	
Q3 (481 pg/mL)	159	-0.08 (-0.23, 0.07)	
Q4 (698 pg/mL)	159	0.15 (0.0, 0.31)	

15.3.B Global score, Rate of decline over 4 Yr

Population: Nurses' Health Study, 1989-2001
Exposure: Plasma vitamin B12
Outcome: Global score, Rate of decline over 4 Yr
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Q1 (272 pg/mL)	158	-	
Q2 (385 pg/mL)	159	-0.01 (-0.06, 0.03)	
Q3 (481 pg/mL)	159	-0.01 (-0.06, 0.03)	
Q4 (698 pg/mL)	159	- (-0.05, 0.05)	

15.3.C Telephone Interview for Cognitive Status (TICS) at first interview

Population: Nurses' Health Study, 1989-2001
Exposure: Plasma vitamin B12
Outcome: Telephone Interview for Cognitive Status (TICS) at first interview
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Q1 (272 pg/mL)	158	-	
Q2 (385 pg/mL)	159	0.38 (-0.17, 0.92)	
Q3 (481 pg/mL)	159	-0.15 (-0.69, 0.39)	
Q4 (698 pg/mL)	159	0.39 (-0.16, 0.95)	

15.3.D Telephone Interview for Cognitive Status (TICS), Rate of decline over 4 Yr

Population: Nurses' Health Study, 1989-2001
Exposure: Plasma vitamin B12
Outcome: Telephone Interview for Cognitive Status (TICS), Rate of decline over 4 Yr
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Q1 (272 pg/mL)	158	-	
Q2 (385 pg/mL)	159	-0.08 (-0.28, 0.12)	
Q3 (481 pg/mL)	159	-0.15 (-0.36, 0.05)	
Q4 (698 pg/mL)	159	-0.1 (-0.31, 0.1)	

15.3.E Verbal score at first interview

Population: Nurses' Health Study, 1989-2001
Exposure: Plasma vitamin B12
Outcome: Verbal score at first interview
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Q1 (272 pg/mL)	158	-	
Q2 (385 pg/mL)	159	0.04 (-0.14, 0.21)	
Q3 (481 pg/mL)	159	-0.16 (-0.33, 0.02)	
Q4 (698 pg/mL)	159	0.08 (-0.1, 0.26)	

15.3.F Verbal score, Rate of decline over 4 Yr

Population: Nurses' Health Study, 1989-2001
Exposure: Plasma vitamin B12
Outcome: Verbal score, Rate of decline over 4 Yr
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Q1 (272 pg/mL)	158	-	
Q2 (385 pg/mL)	159	-0.01 (-0.06, 0.05)	
Q3 (481 pg/mL)	159	-0.01 (-0.07, 0.05)	
Q4 (698 pg/mL)	159	- (-0.06, 0.07)	

Statistical Method(s)

Endpoints: Telephone Interview for Cognitive Status (TICS) at first interview; Global score at first interview; Verbal score at first interview
Adjustment factors: age, age at menopause, alcohol intake, antidepressant use, aspirin use, assay batch, body mass index (BMI), education, history of diabetes, history of high blood pressure, history of high cholesterol, mental health index and energy–fatigue index from the Medical Outcomes Short Form-36, physical activity, postmenopausal hormone use, smoking, time between blood draw and cognitive interview, use of vitamin E supplements
Statistical metric: mean change
Statistical metric description: For the main analysis of performance in the initial cognitive interview, we used linear regression to estimate age- and education-adjusted and multivariable-adjusted mean differences in performance across plasma nutrient quartiles. There was little batch-to-batch variation, and the median values for both nutrients were comparable across batches; thus, we analyzed quartiles created from raw values of folate and vitamin B12 to maximize interpretability of results. In an alternate analysis in which we analyzed quartiles created with batch-specific cut points, we confirmed that the results were nearly identical.

Endpoints: Telephone Interview for Cognitive Status (TICS), Rate of decline over 4 Yr; Global score, Rate of decline over 4 Yr; Verbal score, Rate of decline over 4 Yr
Adjustment factors: age, age at menopause, alcohol intake, antidepressant use, aspirin use, assay batch, body mass index (BMI), education, history of diabetes, history of high blood pressure, history of high cholesterol, mental health index and energy–fatigue index from the Medical Outcomes Short Form-36, physical activity, postmenopausal hormone use, smoking, time between blood draw and cognitive interview, use of vitamin E supplements
Statistical metric: mean change
Statistical metric description: The estimate of the difference in rate of decline from longitudinal analyses (beta x time x folate and beta x time x vitamin B12). For longitudinal analysis using data from a subset of 391 participants who completed all follow-up interviews to date, we used repeated-measures models incorporating random effects for intercepts and slopes. This approach permits description of individual paths of decline and provides explicit tests regarding the relation of exposures to rates of cognitive change.

16. LEVITT, 1992

Full citation: Levitt AJ, Karlinsky H. 1992. Folate, vitamin B12 and cognitive impairment in patients with Alzheimer's disease. Acta Psychiatr Scand 86(4): 301-305.

Funding: None reported

TORONTO GENERAL HOSPITAL REFERRALS, 1989

Age: 71.0 (mean)	**Study design:** Cross-sectional (**n =** 26)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Canada **Region:** Toronto **State:**
Inclusion criteria: referral to Toronto General Hospital's Alzheimer Disease and Related Disorders Clinic, Jan 1989 to Jan 1990	**Exclusion critieria:** cognitively intact, existing delirium

16.1. Exposure: Folate status

Method	Description	Analysis
serum	Blood was drawn within 24 h of initial assessment. Measurement of B12, red cell and serum folate was by radioimmunoassay (Radio-assay Kit).	Levels below the normal range for laboratory were as follows: serum folate <= 54.5 nmol/l; red cell folate <= 270 nmol/l.

Outcomes

	Outcome	Diagnostic Description
A	cognitively impaired not demented (CIND, MMSE >24) (medical professional or test)	A diagnosis of cognitively impaired not demented (CIND) was made when patient demonstrated only mild cognitive deficits as arbitrarily defined as a score of greater than 24 on the MMSE

Results

16.1.A cognitively impaired not demented (CIND, MMSE >24)

Population: Toronto General Hospital, 1989
Exposure: Folate status
Outcome: cognitively impaired not demented (CIND, MMSE >24)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum Folate	25	-0.01	
RBC Folate	24	0.24	

Statistical Method(s)

Endpoints: cognitively impaired not demented (CIND, MMSE >24)
Adjustment factors:
Statistical metric: correlation
Statistical metric description: Pearson correlation coefficient was used to test the bivariate relationship between vitamin levels and MMSE score for each individual group and for the entire sample as a whole.

16.2. Exposure: Vitamin B12 level

Method	Description	Analysis
serum	Blood was drawn within 24 h of initial assessment. Measurement of B12, red cell and serum folate was by radioimmunoassay (Radio-assay Kit).	Levels below the normal range for laboratory were B12 < =140 pmol/l

Outcomes

	Outcome	Diagnostic Description
A	cognitively impaired not demented (CIND, MMSE >24) (medical professional or test)	A diagnosis of cognitively impaired not demented (CIND) was made when patient demonstrated only mild cognitive deficits as arbitrarily defined as a score of greater than 24 on the MMSE

Results

16.2.A <u>cognitively impaired not demented (CIND, MMSE >24)</u>

Population: Toronto General Hospital, 1989
Exposure: Vitamin B12 level
Outcome: cognitively impaired not demented (CIND, MMSE >24)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum vitamin B12	25	-0.03	

Statistical Method(s)

Endpoints: cognitively impaired not demented (CIND, MMSE >24)
Adjustment factors:
Statistical metric: correlation
Statistical metric description: Pearson correlation coefficient was used to test the bivariate relationship between vitamin levels and MMSE score for each individual group and for the entire sample as a whole.

17. MCCRACKEN, 2006

Full citation: McCracken C, Hudson P, Ellis R, McCaddon A. 2006. Methylmalonic acid and cognitive function in the Medical Research Council Cognitive Function and Ageing Study. Am J Clin Nutr 84(6): 1406-1411.

Funding: Supported by a grant from North Wales Research Committee. The epidemiologic investigations were funded by the Medical Research Council as part of the multicenter Cognitive Function and Ageing study (MRC CFA study).

WELSH ELDERLY, COGNITIVE FUNCTION AND AGEING STUDY

Age: 78.0 (median), from 69.0-93.0 years	**Study design:** Cross-sectional (**n =** 84)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** United Kingdom **Region:** North Wales **State:**
Inclusion criteria: >65 years of age, living in own homes	**Exclusion critieria:** study diagnosis of dementia (AGECAT organicity score of O3 or above)

17.1. Exposure: Serum folate and Serum methylmalonic acid (MMA)

Method	Description	Analysis
serum assay	folate concentrations were measured by using an immunoassay analyser (Beckman Coulter Inc, Chaska, MN) -(umol/L) MMA concentrations were quantified by using an in-house gas chromatography–mass spectroscopy method based on the one [described by Rasmussen]--(umol/L)	n/a

Outcomes

	Outcome	Diagnostic Description
A	Abstraction (medical professional or test)	Cognitive Section of the Cambridge Mental Disorders of the Elderly Examination (CAMCOG)- the cognitive battery of the Cambridge examination for mental orders of the elderly
B	Constructional praxis (medical professional or test)	Cognitive Section of the Cambridge Mental Disorders of the Elderly Examination (CAMCOG)- the cognitive battery of the Cambridge examination for mental orders of the elderly
C	Ideational praxis (medical professional or test)	Cognitive Section of the Cambridge Mental Disorders of the Elderly Examination (CAMCOG)- the cognitive battery of the Cambridge examination for mental orders of the elderly
D	Language Comprehension (medical professional or test)	Cognitive Section of the Cambridge Mental Disorders of the Elderly Examination (CAMCOG)- the cognitive battery of the Cambridge examination for mental orders of the elderly

	Outcome	Diagnostic Description
E	Language Expression (medical professional or test)	Cognitive Section of the Cambridge Mental Disorders of the Elderly Examination (CAMCOG)- the cognitive battery of the Cambridge examination for mental orders of the elderly
F	Perception (medical professional or test)	Cognitive Section of the Cambridge Mental Disorders of the Elderly Examination (CAMCOG)- the cognitive battery of the Cambridge examination for mental orders of the elderly
G	Recent memory (medical professional or test)	Cognitive Section of the Cambridge Mental Disorders of the Elderly Examination (CAMCOG)- the cognitive battery of the Cambridge examination for mental orders of the elderly
H	Remote Memory (medical professional or test)	Cognitive Section of the Cambridge Mental Disorders of the Elderly Examination (CAMCOG)- the cognitive battery of the Cambridge examination for mental orders of the elderly
I	Total praxis (medical professional or test)	Cognitive Section of the Cambridge Mental Disorders of the Elderly Examination (CAMCOG)- the cognitive battery of the Cambridge examination for mental orders of the elderly

Results

17.1.A Abstraction

Population: Welsh Elderly, Cognitive Function and Ageing Study
Exposure: Serum folate and Serum methylmalonic acid (MMA)
Outcome: Abstraction
Statistical metric: regression coefficient

Group	N	coefficient 95% CI (low, high)	*p*-value
folate (umol/L)	84	0.27	
MMA (umol/L)	76	-1.2	

17.1.B Constructional praxis

Population: Welsh Elderly, Cognitive Function and Ageing Study
Exposure: Serum folate and Serum methylmalonic acid (MMA)
Outcome: Constructional praxis
Statistical metric: regression coefficient

Group	N	coefficient 95% CI (low, high)	*p*-value
folate (umol/L)	84	0.2	0.05
MMA (umol/L)	76	-0.66	

17.1.C Ideational praxis

Population: Welsh Elderly, Cognitive Function and Ageing Study
Exposure: Serum folate and Serum methylmalonic acid (MMA)
Outcome: Ideational praxis
Statistical metric: regression coefficient

Group	N	coefficient 95% CI (low, high)	*p*-value
folate (umol/L)	84	0.23	0.05
MMA (umol/L)	76	-1.26	0.05

17.1.D Language Comprehension

Population: Welsh Elderly, Cognitive Function and Ageing Study
Exposure: Serum folate and Serum methylmalonic acid (MMA)
Outcome: Language Comprehension
Statistical metric: regression coefficient

Group	N	coefficient 95% CI (low, high)	*p*-value
folate (umol/L)	84	0.11	
MMA (umol/L)	76	-0.85	0.05

17.1.E Language Expression

Population: Welsh Elderly, Cognitive Function and Ageing Study
Exposure: Serum folate and Serum methylmalonic acid (MMA)
Outcome: Language Expression
Statistical metric: regression coefficient

Group	N	coefficient 95% CI (low, high)	*p*-value
folate (umol/L)	84	0.27	
MMA (umol/L)	76	-2.89	0.01

17.1.F Perception

Population: Welsh Elderly, Cognitive Function and Ageing Study
Exposure: Serum folate and Serum methylmalonic acid (MMA)
Outcome: Perception
Statistical metric: regression coefficient

Group	N	coefficient 95% CI (low, high)	*p*-value
folate (umol/L)	84	0.09	
MMA (umol/L)	76	0.04	

17.1.G Recent memory

Population: Welsh Elderly, Cognitive Function and Ageing Study
Exposure: Serum folate and Serum methylmalonic acid (MMA)
Outcome: Recent memory
Statistical metric: regression coefficient

Group	N	coefficient 95% CI (low, high)	*p*-value
folate (umol/L)	84	0.02	
MMA (umol/L)	76	0.29	

17.1.H Remote Memory

Population: Welsh Elderly Cohort, Cognitive Function and Ageing Study
Exposure: Serum folate and Serum methylmalonic acid (MMA)
Outcome: Remote Memory
Statistical metric: adjusted coefficient

Group	N	adjusted coefficient 95% CI (low, high)	*p*-value
folate (umol/L)	84	0.18	0.05

Group	N	adjusted coefficient 95% CI (low, high)	*p*-value
MMA (umol/L)	76	0.05	

17.1.I Total praxis

Population: Welsh Elderly, Cognitive Function and Ageing Study
Exposure: Serum folate and Serum methylmalonic acid (MMA)
Outcome: Total praxis
Statistical metric: regression coefficient

Group	N	coefficient 95% CI (low, high)	*p*-value
folate (umol/L)	84	0.43	0.01
MMA (umol/L)	76	-1.64	0.05

Statistical Method(s)

Endpoints: Language Expression; Constructional praxis; Total praxis; Ideational praxis; Abstraction; Perception; Language Comprehension; Recent memory
Adjustment factors: age, education, serum creatinine, sex
Statistical metric: regression coefficient
Statistical metric description: Regression analysis with missing cases in the dependent and independent variables was achieved by multivariate imputation with the program MICE version 1.14. Regression parameters are presented with their associated SEs in parentheses. An R2 value for goodness-of-fit for the general linear models was calculated as (1 -residual dispersion)/null dispersion and expressed as a percentage.

Endpoints: Remote Memory
Adjustment factors: age, education, serum creatinine, sex
Statistical metric: adjusted coefficient
Statistical metric description: Regression analysis with missing cases in the dependent and independent variables was achieved by multivariate imputation with the program MICE version 1.14. Regression parameters are presented with their associated SEs in parentheses. An R2 value for goodness-of-fit for the general linear models was calculated as (1 -residual dispersion)/null dispersion and expressed as a percentage.

18. MICHELAKOS, 2013

Full citation: Michelakos T, Kousoulis AA, Katsiardanis K, Dessypris N, Anastasiou A, Katsiardani KP, Kanavidis P, Stefanadis C, Papadopoulos FC, Petridou ET. 2013. Serum folate and B12 levels in association with cognitive impairment among seniors: results from the VELESTINO study in Greece and meta-analysis. Journal of aging and health 25(4): 589-616.

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VELESTINO STUDY OF SENIORS

Age: over 65	**Study design:** Cross-sectional (**n =** 593)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Greece **Region:** Velestino **State:**
Inclusion criteria: >65 years of age	**Exclusion critieria:**

18.1. Exposure: Serum B12

Method	Description	Analysis
serum B12	(in pg/mL) Fasting morning blood samples...Folate and B12 levels were assessed in tertiles.	cutoff points for B12 were < 255.6pg/ml and ≥ 371.8pg/ml for males, whereas for females: < 242.1pg/ml and ≥ 366.2pg/ml, respectively

Outcomes

	Outcome	Diagnostic Description
A	Cognitive impairment (medical professional or test)	The validated Greek version of the Mini-Mental State Examination (MMSE) questionnaire was applied and used as a proxy of cognitive impairment. According to the validation protocol, MMSE score < 24 indicates cognitive impairment

Results

18.1.A Cognitive impairment

Population: VELESTINO Study of Seniors
Exposure: Serum B12
Outcome: Cognitive impairment
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
1st (< 255.6) vs 3rd Tertile (≥ 371.8pg/ml)- Male	55	0.88 (0.38, 2.05)	0.77

Group	N	adjOR 95% CI (low, high)	*p*-value
2nd (255.8-371.7)vs. 3rd tertile (≥ 371.8pg/ml)- Male	55	1.04 (0.44, 2.43)	0.93
1st (< 242.1)vs 3rd Tertile (≥ 366.2pg/ml)-Female	82	0.94 (0.44, 2.0)	0.87
2nd (242.1-366.1) vs. 3rd tertile (≥ 366.2pg/ml)-Female	82	0.83 (0.4, 1.71)	0.61

Statistical Method(s)

Endpoints: Cognitive impairment
Adjustment factors: folate status
Statistical metric: adjusted odds ratio
Statistical metric description: A multiple logistic regression core model was thereafter developed with cognitive impairment (MMSE < 24) as the dependent variable and sociodemographic/lifestyle characteristics, BMI and depressive symptoms as independent variables, and the respective adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were estimated. Consequently, serum folate and B12 levels were alternatively introduced as categorical (1st vs 3rd and 2nd vs 3rd tertile) variables (Models 1 and 2, respectively) or simultaneously (Model 3)

18.2. Exposure: Serum folate

Method	Description	Analysis
Serum folate	Fasting morning blood samples have also been collected and determinations were available for serum folate	The cutoff point of the lowest folate tertile was < 4.4ng/ml and of the highest ≥ 7.3ng/ml among males, whereas among females: < 5.5ng/ml and ≥ 8.8ng/ml, respectively

Outcomes

	Outcome	Diagnostic Description
A	Cognitive impairment (medical professional or test)	The validated Greek version of the Mini-Mental State Examination (MMSE) questionnaire was applied and used as a proxy of cognitive impairment. According to the validation protocol, MMSE score < 24 indicates cognitive impairment.

Results

18.2.A Cognitive impairment

Population: VELESTINO Study of Seniors
Exposure: Serum folate
Outcome: Cognitive impairment
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
1st (< 4.4) vs 3rd Tertile (≥ 7.3ng/ml)-Male	55	2.79 (1.17, 6.68)	0.02

Group	N	adjOR 95% CI (low, high)	*p*-value
2nd (4.4-7.2) vs. 3rd tertile (≥ 7.3ng/ml)- Male	55	2.14 (0.92, 5.01)	0.08
1st (< 5.5) vs 3rd Tertile (≥ 8.8ng/ml)-Female	82	1.01 (0.48, 2.15)	0.98
2nd (5.5-8.7) vs. 3rd tertile (≥ 8.8ng/ml)-Female	82	0.83 (0.39, 1.73)	0.61

Statistical Method(s)

Endpoints: Cognitive impairment
Adjustment factors: vitamin B12 status
Statistical metric: adjusted odds ratio
Statistical metric description: A multiple logistic regression core model was thereafter developed with cognitive impairment (MMSE < 24) as the dependent variable and sociodemographic/lifestyle characteristics, BMI and depressive symptoms as independent variables, and the respective adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were estimated. Consequently, serum folate and B12 levels were alternatively introduced as categorical (1st vs 3rd and 2nd vs 3rd tertile) variables (Models 1 and 2, respectively) or simultaneously (Model 3). Model 3 reported here.

19. MILLER, 2009

Full citation: Miller JW, Garrod MG, Allen LH, Haan MN, Green R. 2009. Metabolic evidence of vitamin B-12 deficiency, including high homocysteine and methylmalonic acid and low holotranscobalamin, is more pronounced in older adults with elevated plasma folate. Am J Clin Nutr 90(6): 1586-1592.

Funding: USDA grant 00-35200-9073, SALSA: NIH grant AG12975

ELDERLY LATINOS, SACRAMENTO AREA LATINO STUDY ON AGING (SALSA)

Age: 70.7 (mean)	**Study design:** Cross-sectional (**n =** 1535)
Gender: Male and Female **Ethnicities:** Hispanic/Latino	**Country:** United States **Region:** **State:** California
Inclusion criteria: community dwelling, older than 60 years of age, subjects, their parents, or granparents born in Mexico, Central America, or South America	**Exclusion critieria:**

19.1. Exposure: Plasma vitamin B12 and folate

Method	Description	Analysis
plasma assay	Total plasma vitamin B-12 and plasma folate were measured by radioligand binding assay (Bio-Rad Diagnostics, Hercules, CA); red blood cell (RBC) folate was measured by using automated chemiluminescence (also vitamin supplement use is looked at)	The cutoff value for low plasma vitamin B-12 was defined as 148 pmol/L (standard clinical reerence value), and the cutoff for elevated plasma folate was defined as 45.3 nmol/L (the upper limit of the standard curve for the assay)

Outcomes

	Outcome	Diagnostic Description
A	Center for Epidemiologic Studies Depression Scale (CES-D) (medical professional or test)	Depressive symptoms were assessed on a scale of 0–60 points with the use of the Center for Epidemiologic Studies Depression scale. A score on the Center for Epidemiologic Studies Depression scale 16 is indicative of elevated depressive symptoms.
B	Delayed Recall Test (medical professional or test)	The ability to learn and recall verbal information was assessed on a 0–15-point scale with the use of a delayed recall test. A score >/= 6 on the delayed recall test is indicative of cognitive impairment
C	Modified Mini-Mental State Examination (3MSE) (medical professional or test)	Modified Mini-Mental State Examination (3MSE) was used to assess overall or global cognitive function. The 3MSE evaluates memory, orientation, attention, and language on a scale of 0–100 points. A 3MSE score <=78 is indicative of cognitive impairment.

Results

19.1.A Center for Epidemiologic Studies Depression Scale (CES-D)

Population: Eldery Latinos, Sacramento Area Latino Study on Aging (SALSA)
Exposure: Plasma vitamin B12 and folate
Outcome: Center for Epidemiologic Studies Depression Scale (CES-D)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
VitB12<148 pmol/L; Folate</=45.3 nmol/L	78	-	
VitB12<148 pmol/L; Folate>45.3 nmol/L	22	-	
VitB12>/=148 pmol/L; Folate</=45.3 nmol/L	1055	-	
VitB12>/=148 pmol/L; Folate>45.3 nmol/L	380	-	

19.1.B Delayed Recall Test

Population: Eldery Latinos, Sacramento Area Latino Study on Aging (SALSA)
Exposure: Plasma vitamin B12 and folate
Outcome: Delayed Recall Test
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
VitB12<148 pmol/L; Folate</=45.3 nmol/L	78	-	
VitB12<148 pmol/L; Folate>45.3 nmol/L	22	-	
VitB12>/=148 pmol/L; Folate</=45.3 nmol/L	1055	-	
VitB12>/=148 pmol/L; Folate>45.3 nmol/L	380	-	

19.1.C Modified Mini-Mental State Examination (3MSE)

Population: Eldery Latinos, Sacramento Area Latino Study on Aging (SALSA)
Exposure: Plasma vitamin B12 and folate
Outcome: Modified Mini-Mental State Examination (3MSE)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
VitB12<148 pmol/L; Folate</=45.3 nmol/L	78	-	
VitB12<148 pmol/L; Folate>45.3 nmol/L	22	-	
VitB12>/=148 pmol/L; Folate</=45.3 nmol/L	1055	-	
VitB12>/=148 pmol/L; Folate>45.3 nmol/L	380	-	0.02

Statistical Method(s)

Endpoints: Modified Mini-Mental State Examination (3MSE); Center for Epidemiologic Studies Depression Scale (CES-D); Delayed Recall Test
Adjustment factors: age, educational achievement, plasma creatinine, sex, supplement use
Statistical metric: other
Statistical metric description: A Scheffe test was used to compare mean values among the groups for age, all blood analytes, both cognitive function scores, and depressive symptom score. Chi-square analysis was used to compare sex distributions, percentage of supplement users, percentage with low cognitive function scores, and percentage with elevated depressive symptoms among the groups. Interactions between total plasma vitamin B-12 (low and nonlow) and plasma folate (nonelevated and elevated) …. assessed by 2- factor analysis of variance.

20. MILLS, 2011

Full citation: Mills JL, Carter TC, Scott JM, Troendle JF, Gibney ER, Shane B, Kirke PN, Ueland PM, Brody LC, Molloy AM. 2011. Do high blood folate concentrations exacerbate metabolic abnormalities in people with low vitamin B-12 status? Am J Clin Nutr 94(2): 495-500.

Funding: Supported by the Intramural Research Program of the National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

IRISH UNIVERSITY STUDENTS, 2003-2004

Age: 22.5 (mean)	**Study design:** Cross-sectional (**n =** 2507)
Gender: Male and Female **Ethnicities:** White	**Country:** Ireland **Region:** Dublin **State:**
Inclusion criteria: Irish grandparents, no major medical problems, students at University of Dublin, Trinity College	**Exclusion critieria:**

20.1. Exposure: Vitamin B12 and folate status

Method	Description	Analysis
serum assays	Serum folate, red blood cell folate (RCF), and serum vitamin B-12 were measured by microbiological assays as previously described ...	Concentrations of serum vitamin B-12 <148 pmol/L and serum folate >30 nmol/L (group 1) and subjects with concentrations of serum vitamin B-12 <148 pmol/L and serum folate</=30 nmol/L (group 2)

Outcomes

	Outcome	Diagnostic Description
A	Mean change Serum methylmalonic acid (umol/L) (medical professional or test)	gas chromatography–mass spectrometry
B	Serum methylmalonic acid >0.26 umol/L cutoff (medical professional or test)	above or below 0.26 umol/L of serum MMA (measured by gas chromatography–mass spectrometry)
C	Serum methylmalonic acid level (medical professional or test)	Serum methylmalonic acid (umol/L) measured by gas chromatography–mass spectrometry

Results

20.1.A <u>Mean change Serum methylmalonic acid (umol/L)</u>

Population: Irish University Students
Exposure: Vitamin B12 and folate status
Outcome: Mean change Serum methylmalonic acid (umol/L)
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
(group 1) vitamin B-12 <148 pmol/L; folate > 30 nmol/L	43	-	0.12
(group 2) vitamin B-12 <148 pmol/L; folate <=30 nmol/L	85	-	

20.1.B Serum methylmalonic acid >0.26 umol/L cutoff

Population: Irish University Students, 2003-2004
Exposure: Vitamin B12 and folate status
Outcome: Serum methylmalonic acid >0.26 umol/L cutoff
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
(group 1) vitamin B-12 <148 pmol/L; folate > 30 nmol/L	43	-	0.33
(group 2) vitamin B-12 <148 pmol/L; folate <=30 nmol/L	85	-	

20.1.C Serum methylmalonic acid level

Population: Irish University Students, 2003-2004
Exposure: Vitamin B12 and folate status
Outcome: Serum methylmalonic acid level
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
(group 1) vitamin B-12 <148 pmol/L; folate > 30 nmol/L	43	-	0.057
(group 2) vitamin B-12 <148 pmol/L; folate <=30 nmol/L	85	-	

Statistical Method(s)

Endpoints: Mean change Serum methylmalonic acid (umol/L)
Adjustment factors: MTHFR genotype, age, alcohol intake, plasma creatinine, serum ferritin, sex, smoking
Statistical metric: mean change
Statistical metric description: Adjusted median differences of biomarker concentrations between groups 1 and 2 were compared by fitting linear regression to Box-Cox–transformed values of biomarker concentrations that were outcome measures

Endpoints: Serum methylmalonic acid >0.26 umol/L cutoff
Adjustment factors: MTHFR genotype, age, alcohol intake, plasma creatinine, serum ferritin, sex, smoking
Statistical metric: other
Statistical metric description: the chi-square and Fisher's exact tests were used for categorical variables... Adjusted median differences of biomarker concentrations between groups 1 and 2 were compared by fitting linear regression to Box-Cox–transformed values of biomarker concentrations that were outcome measures

Endpoints: Serum methylmalonic acid level
Adjustment factors: age, alcohol intake, plasma creatinine, serum ferritin, sex, smoking
Statistical metric: mean
Statistical metric description: Adjusted median differences of biomarker concentrations between groups 1 and 2 were compared by fitting linear regression to Box-Cox–transformed valuesof biomarker concentrations that were outcome measures

21. MOORE, 2014

Full citation: Moore EM, Ames D, Mander AG, Carne RP, Brodaty H, Woodward MC, Boundy K, Ellis KA, Bush AI, Faux NG, Martins RN, Masters CL, Rowe CC, Szoeke C, Watters DA. 2014. Among vitamin B12 deficient older people, high folate levels are associated with worse cognitive function: combined data from three cohorts. J Alzheimers Dis 39(3): 661-668.

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PROSPECTIVE RESEARCH IN MEMORY (PRIME) & THE AUSTRALIAN IMAGING, BIOMARKERS AND LIFESTYLE (AIBL), AUSTRALIA

Age: 73.7 (mean)	**Study design:** Cross-sectional (**n =** 1354)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Australia **Region:** Barwon **State:**
Inclusion criteria: patients with Alzheimer's Disease or cognitive impairment	**Exclusion critieria:** stroke or neurodegenerative diseases other than Alzheimer's disease

21.1. Exposure: Red cell folate and serum vitamin B12

Method	Description	Analysis
assay	Serum vitamin B12 and RCF levels were measured using the ADVIA Centaur chemiluminescent microparticle immunoassay at most sites. Exceptions were as follows: Prime Site 2 used the Tosoh immunoassay analyser AIA600, Prime Site 4 used the Roche Cobas 8000 electrochemiluminescence immunoassay, and Prime Site 6 used a Siemens Healthcare Diagnostic Immulite 2000 immunoassay.	m vitamin B12 measurements below 250 pmol/L were considered 'low'; whereas measurements of 250 pmol/L or higher were considered 'normal'. Red cell folate (RCF) measurements in the 90th percentile (>1,594 nmol/L) were considered 'high', whereas RCF levels of 1,594 nmol/L or lower were considered 'normal'. These cut-offs for biochemical marker status approximate those used by the Framingham Heart Study investigators.

Outcomes

	Outcome	Diagnostic Description
A	Cognitive impairment (medical professional or test)	A Mini-Mental State Examination score of <24 was used to define impaired cognitive function

Results

21.1.A Cognitive impairment

Population: Cognitive impairment Prospective Research in Memory (PRIME) & The Australian Imaging, Biomarkers and Lifestyle (AIBL), Australia
Exposure: Red cell folate and serum vitamin B12
Outcome: Cognitive impairment
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Folate </= 1,594 nmol/L, B12 >/=250 pmol/L	742	1.0	
Folate >1,594 nmol/L, B12 >/=250 pmol/L	97	1.74 (1.03, 2.95)	0.04
Folate </=1,594 nmol/L, B12 <250 pmol/L	476	1.85 (1.37, 2.5)	0.001
Folate >1,594 nmol/L, B12 <250 pmol/L	39	3.45 (1.6, 7.43)	0.002

Statistical Method(s)

Endpoints: Cognitive impairment
Adjustment factors: age (ten-year age groups), history of depression, level of education (primary, secondary, or tertiary)
Statistical metric: adjusted odds ratio
Statistical metric description: A binary logistic regression model was formed with cognitive performance

as the response variable. The MMSE is sensitive to age, level of education, and depression, so the model was adjusted for these variables.

22. MORRIS, 2005

Full citation: Morris MC, Evans DA, Bienias JL, Tangney CC, Hebert LE, Scherr PA, Schneider JA. 2005. Dietary folate and vitamin B12 intake and cognitive decline among community-dwelling older persons. Arch Neurol 62(4): 641-645.

Funding: This study was supported by grants AG11101 and AG13170 from the National Institute on Aging, Bethesda, Md.

CHICAGO HEALTH AND AGING PROJECT (CHAP), 1993-2002

Age: means of folate quintiles: 74.3; 74.0; 74.2; 74.9; 74.5	**Study design:** Prospective (**n =** 3718)
Gender: Male and Female **Ethnicities:** Black or African American, White	**Country:** United States **Region:** Chicago **State:** Illinois
Inclusion criteria: >65 years of age	**Exclusion critieria:** food frequency questionnaire completed >2.5 years after baseline, potentially invalid food frequency questionnaire data, residing in 3 neighborhoods in Chicago, Ill

22.1. Exposure: Folate from food

Method	Description	Analysis
questionnaire	Diet was assessed using a modified Harvard FFQ13 that inquired about usual intake during the past year of 139 food items ... Post-1997 estimates of folate intake reflect the folate fortification	Nutrient composition for each food was multiplied by frequency of intake and summed over all food items to estimate daily nutrient intake. All nutrients were energy adjusted using the regression residual method. plus validated against 24-hr recalls

Outcomes

	Outcome	Diagnostic Description
A	Change in Cognition Score During 6 years (medical professional or test)	The 4 cognitive tests included the East Boston Tests of immediate and delayed recall (0 to 12 ideas recalled),16 the MiniMental State Examination (0 to 30 correct items),17 and the Symbol Digit Modalities Test18 of perceptual speed and attention (0 to 96 correct items). We computed z scores for the 4 tests and averaged the scores for a global measure of cognitive function.

Results

22.1.A Change in Cognition Score During 6 years

Population: Chicago Health and Aging Project (CHAP), 1993-2002
Exposure: Folate from food

Outcome: Change in Cognition Score During 6 years
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Q1 (175 ug/d)	-	-	
Q2 (227 ug/d)	-	-0.01	0.04
Q3 (268 ug/d)	-	-0.01	0.06
Q4 (312 ug/d)	-	-0.01	0.06
Q5 (382 ug/d)	-	-0.02	0.02

Statistical Method(s)

Endpoints: Change in Cognition Score During 6 years
Adjustment factors: age, educational achievement, multivitamin use (yes or no), quintiles of folate intake, race-ethnicity, sex, time, time interactions with age and quintiles of folate intake, time interactions with all covariates, total vitamin C intake, vitamin E intake from food
Statistical metric: adjusted beta
Statistical metric description: We used mixed-effects models in SAS statistical software to estimate effects of vitamin B12 and folate on the annual rate of change in cognitive score. The model explicitly accounts for individual differences in initial level of cognition and its correlation with rate of change. Energy-adjusted folate and vitamin B12 intakes were modeled in quintiles. Other energy-adjusted nutrients were modeled as continuous log-transformed variables. Model coefficients (Beta) represent the difference in slopes (rates of cognitive change per year) for an upper quintile of intake compared with the referent lowest quintile. Effect modification was examined by including terms in the model for all 2-way and 3-way interaction terms among the covariate, intake of folate or vitamin B12, and time.

22.2. Exposure: Folate supplement dose

Method	Description	Analysis
questionnaire	Folate Vitamin Supplementation measured by modified Harvard FFQ that inquired about usual intake during the past year of 139 food items and vitamin supplements.	All nutrients were energy adjusted using the regression residual method. In a validation study of 232 randomly selected CHAP participants using repeated 24-hour dietary recalls as a comparison, correlations were 0.70 and 0.50 for total folate reproducibility and validity, respectively

Outcomes

	Outcome	Diagnostic Description
A	Change in Cognition Score During 6 years (medical professional or test)	The 4 cognitive tests included the East Boston Tests of immediate and delayed recall (0 to 12 ideas recalled),16 the MiniMental State Examination (0 to 30 correct items),17 and the Symbol Digit Modalities Test18 of perceptual speed and attention (0 to 96 correct items). We computed z scores for the 4 tests and averaged the scores for a global measure of cognitive function.

Results

22.2.A Change in Cognition Score During 6 years

Population: Chicago Health and Aging Project (CHAP), 1993-2002
Exposure: Folate supplement dose
Outcome: Change in Cognition Score During 6 years
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Nonusers	2541	-	
1-200 ug/day	224	-0.01	0.25
201-399 ug/day	303	-0.01	0.18
400 ug/day	380	-0.01	0.22
401-1200 ug/day	270	-0.03	0.001

Statistical Method(s)

Endpoints: Change in Cognition Score During 6 years
Adjustment factors: age, educational achievement, quintiles of folate intake, race-ethnicity, sex, time, time interactions with age and quintiles of folate intake, time interactions with all covariates, total vitamin C intake, vitamin E intake from food
Statistical metric: adjusted beta
Statistical metric description: We used mixed-effects models in SAS statistical software to estimate effects of vitamin B12 and folate on the annual rate of change in cognitive score. The model explicitly accounts for individual differences in initial level of cognition and its correlation with rate of change. Energy-adjusted folate and vitamin B12 intakes were modeled in quintiles. Other energy-adjusted nutrients were modeled as continuous log-transformed variables. Model coefficients (Beta) represent the difference in slopes (rates of cognitive change per year) for an upper quintile of intake compared with the referent lowest quintile. Effect modification was examined by including terms in the model for all 2-way and 3-way interaction terms among the covariate, intake of folate or vitamin B12, and time.

22.3. Exposure: Total folate

Method	Description	Analysis
questionnaire	Diet was assessed using a modified Harvard FFQ that inquired about usual intake during the past year of 139 food items and vitamin supplements. Post-1997 estimates of folate intake reflect the folate fortification.	Nutrient composition for each food was multiplied by frequency of intake and summed over all food items to estimate daily nutrient intake

Outcomes

	Outcome	Diagnostic Description
A	Change in Cognition Score During 6 years (medical professional or test)	The 4 cognitive tests included the East Boston Tests of immediate and delayed recall (0 to 12 ideas recalled),16 the MiniMental State Examination (0 to 30 correct items),17 and the Symbol Digit Modalities Test18 of perceptual speed and attention (0 to 96 correct

	Outcome	Diagnostic Description
		items). We computed z scores for the 4 tests and averaged the scores for a global measure of cognitive function.

Results

22.3.A Change in Cognition Score During 6 years

Population: Chicago Health and Aging Project (CHAP), 1993-2002
Exposure: Total folate
Outcome: Change in Cognition Score During 6 years
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Q1 (186 ug/d)	-	-	
Q2 (251 ug/d)	-	-0.01	0.41
Q3 (311 ug/d)	-	-0.01	0.38
Q4 (419 ug/d)	-	-0.02	0.04
Q5 (742 ug/d)	-	-0.02	0.002

Statistical Method(s)

Endpoints: Change in Cognition Score During 6 years
Adjustment factors: age, educational achievement, multivitamin use (yes or no), quintiles of folate intake, race-ethnicity, sex, time, time interactions with age and quintiles of folate intake, time interactions with all covariates, total vitamin C intake, vitamin E intake from food
Statistical metric: adjusted beta
Statistical metric description: We used mixed-effects models in SAS statistical software to estimate effects of vitamin B12 and folate on the annual rate of change in cognitive score. The model explicitly accounts for individual differences in initial level of cognition and its correlation with rate of change. Energy-adjusted folate and vitamin B12 intakes were modeled in quintiles. Other energy-adjusted nutrients were modeled as continuous log-transformed variables. Model coefficients (Beta) represent the difference in slopes (rates of cognitive change per year) for an upper quintile of intake compared with the referent lowest quintile. Effect modification was examined by including terms in the model for all 2-way and 3-way interaction terms among the covariate, intake of folate or vitamin B12, and time.

22.4. Exposure: Vitamin B12 intake

Method	Description	Analysis
questionnaire	FFQ (see folate)	see folate

Outcomes

	Outcome	Diagnostic Description
A	Change in Cognition Score During 6 years (medical professional or test)	The 4 cognitive tests included the East Boston Tests of immediate and delayed recall (0 to 12 ideas recalled),16 the MiniMental State Examination (0 to 30 correct items),17 and the Symbol Digit Modalities Test18 of perceptual speed and attention (0 to 96 correct items). We computed z scores for the 4 tests and averaged the scores for a global measure of cognitive function.

Results

22.4.A Change in Cognition Score During 6 years

Population: Chicago Health and Aging Project (CHAP), 1993-2002
Exposure: Vitamin B12 intake
Outcome: Change in Cognition Score During 6 years
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Vitamin b12 intake	-	-	

Statistical Method(s)

Endpoints: Change in Cognition Score During 6 years
Adjustment factors: age, educational achievement, multivitamin use (yes or no), quintiles of folate intake, race-ethnicity, sex, time, time interactions with age and quintiles of folate intake, time interactions with all covariates, total vitamin C intake, vitamin E intake from food
Statistical metric: adjusted beta
Statistical metric description: We used mixed-effects models in SAS statistical software to estimate effects of vitamin B12 and folate on the annual rate of change in cognitive score. The model explicitly accounts for individual differences in initial level of cognition and its correlation with rate of change. Energy-adjusted folate and vitamin B12 intakes were modeled in quintiles. Other energy-adjusted nutrients were modeled as continuous log-transformed variables. Model coefficients (Beta) represent the difference in slopes (rates of cognitive change per year) for an upper quintile of intake compared with the referent lowest quintile. Effect modification was examined by including terms in the model for all 2-way and 3-way interaction terms among the covariate, intake of folate or vitamin B12, and time.

23. MORRIS, 2007

Full citation: Morris MS, Jacques PF, Rosenberg IH, Selhub J. 2007. Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr 85(1): 193-200.

Funding: Supported by USDA agreement no. 58-1950-9-001 and NIH no. R03 AG021536-01.

NHANES 1999 –2002

Age: 70.0 (mean)	**Study design:** Cross-sectional (**n =** 1459)
Gender: Male and Female **Ethnicities:** Other, Black or African American, Hispanic/Latino, White	**Country:** United States **Region:** national **State:**
Inclusion criteria: older than 60 years of age	**Exclusion critieria:** history of stroke or diseases of the liver, thyroid, or coronary arteries, recent anemia therapy, those with serum creatinine concentrations indicative of renal dysfunction

23.1. Exposure: Folate and B-12 status

Method	Description	Analysis
serum	Serum concentrations of folate and vitamin B-12 were measured by using the Quantaphase II Radioassay Kit (Bio-Rad Laboratories, Anaheim, CA).	Low serum vitamin B-12 status defined as a concentration 148 pmol/L or a serum methylmalonic acid concentration above the reference range (ie, 60 –210 nmol/L) for serum vitamin B-12–replete participants with normal serum creatinine. High status defined as a serum folate concentration 59 nmol/L (80th percentile).

Outcomes

	Outcome	Diagnostic Description
A	Cognitive impairment, digit symbol-coding score <34 (medical professional or test)	The cognitive function of seniors was assessed by using a version of the Digit Symbol-Coding subtest of the Wechsler Adult Intelligence Scale III. In the test, participants copy symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant draws the symbol under the corresponding number. The score is the number of correct symbols drawn within 120 s. One point is given for each correctly drawn symbol completed within the time limit for a maximum score of 133. The study defined cognitive impairment as having attained a test score less than 34, the 20th percentile of the distribution.

Results

23.1.A Cognitive impairment, digit symbol-coding score <34

Population: NHANES 1999-2002, age over 60
Exposure: Folate and B-12 status
Outcome: Cognitive impairment, digit symbol-coding score <34
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Norm/Norm (B12 >=148pmol/L; Folate <=59nmol/L)	826	1.0	
Norm/High (B12 >=148pmol/L; Folate >59nmol/L)	180	0.5 (0.2, 0.96)	0.05
Low/Norm (B12 <148pmol/L; Folate <=59nmol/L)	253	1.6 (0.95, 2.8)	
Low/High (B12 <148pmol/L; Folate >59nmol/L)	42	4.9 (2.6, 9.2)	0.05

Statistical Method(s)

Endpoints: Cognitive impairment, digit symbol-coding score <34
Adjustment factors: age, educational achievement, hyperhomocysteinemia, race-ethnicity, self-reported history of cancer, diabetes, alcohol abuse, serum creatinine, serum ferritin, serum glucose, sex
Statistical metric: adjusted odds ratio
Statistical metric description:

24. MORRIS, 2010

Full citation: Morris MS, Jacques PF, Rosenberg IH, Selhub J. 2010. Circulating unmetabolized folic acid and 5-methyltetrahydrofolate in relation to anemia, macrocytosis, and cognitive test performance in American seniors. Am J Clin Nutr 91(6): 1733-1744.

Funding: Supported by USDA agreement no. 58-1950-7-707 and USDA grant 2006-35200-17198.

SENIORS, NHANES (1999-2002)

Age: 70.5 (mean)	**Study design:** Cross-sectional (**n =** 1858)
Gender: Male and Female **Ethnicities:** Two or More Races	**Country:** United States **Region:** **State:**
Inclusion criteria: seniors over 60 years	**Exclusion critieria:** history of stroke or diseases of the liver, thyroid, or coronary arteries, recent anemia therapy, those with serum creatinine concentrations indicative of renal dysfunction

24.1. Exposure: 5-methyltetrahydrofolate (5MeTHF)

Method	Description	Analysis
biochemical assay of serum	We measured ... 5MeTHF at the Jean Mayer Human Nutrition Research Center on Aging (HNRCA) at Tufts University using a modification of the affinity/HPLC with electrochemical (coulometric) detection method previously developed at the HNRCA	The limit of detection was 0.18nmol/L of detectable circulating unmetabolized folic acid (original paper states 0.027 nmol/L, but Erratum states corrects this to 0.18nmol/L)

Outcomes

	Outcome	Diagnostic Description
A	Digit-Symbol Substitution Test (DSST) (medical professional or test)	The version of the Digit-Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale III—a screening test designed to detect cognitive impairment in adults and children. In the test, participants copy symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant draws the symbol under the corresponding number. The score, which declines with age (38), is the number of correct symbols drawn within 120 s. One point is given for each correctly drawn symbol completed within the time limit for a maximum score of 133.Use of the test in the 1999–2002 NHANES was based on its reputation as a more sensitive measure of dementia than the Mini-Mental State Examination. we classified subjects as having performed poorly or well using a score of 34—the 20th percentile of the distribution—as the cutoff between the 2 categories

Results

24.1.A Digit-Symbol Substitution Test (DSST)

Population: Seniors, NHANES (1999-2002)
Exposure: 5-methyltetrahydrofolate (5MeTHF)
Outcome: Digit-Symbol Substitution Test (DSST)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
5MeTHF	1611	-	0.003

Statistical Method(s)

Endpoints: Digit-Symbol Substitution Test (DSST)
Adjustment factors: age, race-ethnicity, sex
Statistical metric: other
Statistical metric description: To graphically illustrate the trend in DSST scores with increasing 5MeTHF concentration in subjects with normal vitamin B-12 status, we used SUDAAN PROC REGRESS to estimate least-squares mean (95% CI) DSST scores for quintile categories of serum 5MeTHF using the multivariate model described above for this outcome

24.2. Exposure: 5MeTHF, interaction with Vitamin B12 status

Method	Description	Analysis
serum assay	Unmetabolized 5MeTHF in serum were measured by using affinity/HPLC with electrochemical (coulometric) detection.	We measured 5MeTHF at the Jean Mayer Human Nutrition Research Center on Aging (HNRCA) at Tufts University using a modification of the affinity/HPLC with electrochemical (coulometric) detection method previously developed at the HNRCA (27).

Outcomes

	Outcome	Diagnostic Description
A	Cognitive Score on Digit-Symbol Substitution Test (DSST) (medical professional or test)	version of the Digit-Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale III—a screening test designed to detect cognitive impairment in adults and children ...Use of the test in the 1999–2002 NHANES was based on its reputation as a more sensitive measure of dementia than the Mini-Mental State Examination

Results

24.2.A Cognitive Score on Digit-Symbol Substitution Test (DSST)

Population: Seniors, NHANES (1999-2002)
Exposure: 5MeTHF, interaction with Vitamin B12 status
Outcome: Cognitive Score on Digit-Symbol Substitution Test (DSST)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
5MeTHF, in Low B12	-	-0.03 (-0.1, 0.04)	0.408
5MeTHF, in Normal B12	-	0.07 (0.04, 0.11)	0.001

Statistical Method(s)

Endpoints: Cognitive Score on Digit-Symbol Substitution Test (DSST)
Adjustment factors: age, current smoking status, educational achievement, race-ethnicity, self-reported history of cancer, diabetes, alcohol abuse, serum concentration of C-reactive protein, serum concentration of cystatin C, sex
Statistical metric: adjusted beta
Statistical metric description: To graphically illustrate the trend in DSST scores with increasing 5MeTHF concentration in subjects with normal vitamin B-12 status we used SUDAAN PROC REGRESS to estimate least-squares mean (95% CI) DSST scores for quintile categories of serum 5MeTHF using the multivariate model described above for this outcome

24.3. Exposure: Dietary Folic Acid Intake

Method	Description	Analysis
interview	2001–2002 NHANES data; The dietary data were collected in a single 24-h dietary-recall interview administered by trained staff during the MEC examination.	The US Department of Agriculture (USDA) was responsible for the survey's dietary data collection methods, maintenance of the databases used to code and process the data, and data review and processing. The USDA National Nutrient Database for Standard Reference Dietary Studies (version 1) was used to calculate daily nutrient intakes from food, including folic acid intake from fortified food. These values were additionally adjusted for food folate.

Outcomes

	Outcome	Diagnostic Description
A	Digit-Symbol Substitution Test (DSST) (medical professional or test)	The version of the Digit-Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale III—a screening test designed to detect cognitive impairment in adults and children. In the test, participants copy symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant draws the symbol under the corresponding number. The score, which declines with age (38), is the number of correct symbols drawn within 120 s. One point is given for each correctly drawn symbol completed within the time limit for a maximum score of 133.Use of the test in the 1999–2002 NHANES was based on its reputation as a more sensitive measure of dementia than the Mini-Mental State Examination. we classified subjects as having performed poorly or

	Outcome	Diagnostic Description
		well using a score of 34—the 20th percentile of the distribution—as the cutoff between the 2 categories

Results

24.3.A Digit-Symbol Substitution Test (DSST)

Population: Seniors, NHANES (1999-2002)
Exposure: Dietary Folic Acid Intake
Outcome: Digit-Symbol Substitution Test (DSST)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Dietary Folic Acid Intake	1611	-	0.02

Statistical Method(s)

Endpoints: Digit-Symbol Substitution Test (DSST)
Adjustment factors: age, race-ethnicity, sex
Statistical metric: other
Statistical metric description: To graphically illustrate the trend in DSST scores with increasing 5MeTHF concentration in subjects with normal vitamin B-12 status, we used SUDAAN PROC REGRESS to estimate least-squares mean (95% CI) DSST scores for quintile categories of serum 5MeTHF using the multivariate model described above for this outcome.

24.4. Exposure: Folate intake

Method	Description	Analysis
NHANES survey data from 2001-2002	the dietary data were collected in a single 24-h dietary-recall interview administered by trained staff during the MEC examination	The USDA National Nutrient Database for Standard Reference Dietary Studies (version 1) was used to calculate daily nutrient intakes from food, including folic acid intake from fortified foods

Outcomes

	Outcome	Diagnostic Description
A	Digit-Symbol Substitution Test (DSST) (medical professional or test)	The version of the Digit-Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale III—a screening test designed to detect cognitive impairment in adults and children. In the test, participants copy symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant draws the symbol under the corresponding number. The score, which declines with age (38), is the number of correct symbols drawn within 120 s. One point is given for each correctly drawn symbol completed within the time limit for a maximum score of 133.Use of the test in the 1999–2002 NHANES was based on its reputation as a more sensitive measure of dementia than the Mini-Mental State Examination. we classified subjects as having performed poorly or

	Outcome	Diagnostic Description
		well using a score of 34—the 20th percentile of the distribution—as the cutoff between the 2 categories

Results

24.4.A Digit-Symbol Substitution Test (DSST)

Population: Seniors, NHANES (1999-2002)
Exposure: Folate intake
Outcome: Digit-Symbol Substitution Test (DSST)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folate intake	1611	-	0.001

Statistical Method(s)

Endpoints: Digit-Symbol Substitution Test (DSST)
Adjustment factors: age, race-ethnicity, sex
Statistical metric: other
Statistical metric description: To graphically illustrate the trend in DSST scores with increasing 5MeTHF concentration in subjects with normal vitamin B-12 status, we used SUDAAN PROC REGRESS to estimate least-squares mean (95% CI) DSST scores for quintile categories of serum 5MeTHF using the multivariate model described above for this outcome

24.5. Exposure: Folic acid user

Method	Description	Analysis
in-home interview	Data on dietary supplement use were collected during the in-home interview.. Subjects were asked whether they had used any vitamins, minerals, or other dietary supplements within 30 d of the interview. Subjects who had used such products were asked to show the interviewer the supplement containers and provide information on the amount, frequency, and duration of use.	The amount of each ingredient in each product used was determined by matching the name and manufacturer of the supplement to those in a database developed by the National Center for Health Statistics in collaboration with the National Institutes of Health's Office of Dietary Supplements.

Outcomes

	Outcome	Diagnostic Description
A	Digit-Symbol Substitution Test (DSST) (medical professional or test)	The version of the Digit-Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale III—a screening test designed to detect cognitive impairment in adults and children. In the test, participants copy symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant draws the symbol under the corresponding number. The score, which

	Outcome	Diagnostic Description
		declines with age (38), is the number of correct symbols drawn within 120 s. One point is given for each correctly drawn symbol completed within the time limit for a maximum score of 133.Use of the test in the 1999–2002 NHANES was based on its reputation as a more sensitive measure of dementia than the Mini-Mental State Examination. we classified subjects as having performed poorly or well using a score of 34—the 20th percentile of the distribution—as the cutoff between the 2 categories

Results

24.5.A Digit-Symbol Substitution Test (DSST)

Population: Seniors, NHANES (1999-2002)
Exposure: Folic acid user
Outcome: Digit-Symbol Substitution Test (DSST)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folic acid supplement users	1611	-	

Statistical Method(s)

Endpoints: Digit-Symbol Substitution Test (DSST)
Adjustment factors: age, race-ethnicity, sex
Statistical metric: other
Statistical metric description: n/a

24.6. Exposure: Serum total folate, interaction with Vitamin B12 status

Method	Description	Analysis
serum measure	Quantaphase II Radioassay Kit: These priority analyses included measurement of serum concentrations of vitamin B-12 and folate, which were carried out by using the Quantaphase II Radioassay Kit (Bio-Rad Laboratories, Anaheim, CA.) HPLC: Tufts University using a modification of the affinity/HPLC with electrochemical (coulometric) detection method previously developed at the HNRCA. Low vitamin B-12 status was defined as a serum vitamin B-12 concentration <148 pmol/L. We measured folic acid and 5MeTHF at the Jean Mayer Human Nutrition Research Center on Aging (HNRCA) at Tufts University using a modification of the affinity/HPLC with electrochemical (coulometric) detection method previously developed at the HNRCA (27). Although serum total folate includes not only folic acid and 5MeTHF, but also 5-formyl-THF (43), which we did not measure, we used the terms "radioassay-determined serum total folate" and "HPLC-determined serum total folate" in this report to distinguish the radioassay-determined values from the sum of the HPLC-determined folic acid and 5MeTHF concentrations.	The limit of detection was 0.18nmol/L of detectable circulating unmetabolized folic acid (original paper states 0.027 nmol/L, but Erratum states corrects this to 0.18nmol/L)

Outcomes

	Outcome	Diagnostic Description
A	Low Digit-Symbol Substitution Test (DSST) Score (medical professional or test)	The version of the Digit-Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale III—a screening test designed to detect cognitive impairment in adults and children. In the test, participants copy symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant draws the symbol under the corresponding number. The score, which declines with age (38), is the number of correct symbols drawn within 120 s. One point is given for each correctly drawn symbol completed within the time limit for a maximum score of 133.we classified subjects as having performed poorly or well using a score of 34—the 20th percentile of the distribution—as the cutoff between the 2 categories

Results

24.6.A Low Digit-Symbol Substitution Test (DSST) Score

Population: Seniors, NHANES (1999-2002)
Exposure: Serum total folate, interaction with Vitamin B12 status
Outcome: Low Digit-Symbol Substitution Test (DSST) Score
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
serum folate >75th%ile, in low B12 (Radioassay)	-	2.02 (1.1, 3.71)	0.026
serum folate >75th%ile, in normal B12 (Radioassay)	-	0.49 (0.28, 0.85)	0.013
serum folate >75th%ile, in low B12 (HPLC)	-	2.12 (1.03, 4.38)	0.042
serum folate >75th%ile, in normal B12 (HPLC)	-	0.77 (0.44, 1.36)	0.631

Statistical Method(s)

Endpoints: Low Digit-Symbol Substitution Test (DSST) Score
Adjustment factors: age, current smoking status, educational achievement, race-ethnicity, serum concentration of C-reactive protein, serum concentration of cystatin C, sex
Statistical metric: adjusted odds ratio
Statistical metric description: To facilitate comparison between the results of our current investigation, in which folate fractions were measured by using HPLC, and the findings we aimed to clarify, which were based on radioassay-determined serum total folate, we also considered how vitamin B-12 status interacted with both radioassay-determined serum total folate and HPLC-determined serum total folate in relation to the odds of anemia, macrocytosis, and a low compared with a higher DSST score. We conducted these analyses by using multiple logistic regression as performed by SUDAAN PROC RLOGIST, and we defined high serum total folate as a value above the 75th percentile (ie, radioassay: 55 nmol/L; HPLC: 66 nmol/L).

24.7. Exposure: Unmetabolized folic acid, interaction with Vitamin B12 status

Method	Description	Analysis
serum assay	Unmetabolized folic acid ...in serum were measured by using affinity/HPLC with electrochemical (coulometric) detection.	The limit of detection was 0.18nmol/L of detectable circulating unmetabolized folic acid (original paper states 0.027 nmol/L, but Erratum states corrects this to 0.18nmol/L)

Outcomes

	Outcome	Diagnostic Description
A	Cognitive Score on Digit-Symbol Substitution Test (DSST) (medical professional or test)	version of the Digit-Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale III—a screening test designed to detect cognitive impairment in adults and children ...Use of the test in the

	Outcome	Diagnostic Description
		1999–2002 NHANES was based on its reputation as a more sensitive measure of dementia than the Mini-Mental State Examination

Results

24.7.A Cognitive Score on Digit-Symbol Substitution Test (DSST)

Population: Seniors, NHANES (1999-2002)
Exposure: Unmetabolized folic acid, interaction with Vitamin B12 status
Outcome: Cognitive Score on Digit-Symbol Substitution Test (DSST)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Unmetabolized folic acid, in Low B12	-	-4.86 (-9.09, -0.63)	0.026
Unmetabolized folic acid, in Normal B12	-	2.05 (-0.6, 4.7)	0.125

Statistical Method(s)

Endpoints: Cognitive Score on Digit-Symbol Substitution Test (DSST)
Adjustment factors: age, current smoking status, educational achievement, race-ethnicity, self-reported history of cancer, diabetes, alcohol abuse, serum concentration of C-reactive protein, serum concentration of cystatin C, sex
Statistical metric: adjusted beta
Statistical metric description: We also considered how vitamin B-12 status interacted with both radioassay-determined serum total folate and HPLC-determined serum total folate in relation to the odds of anemia, macrocytosis, and a low compared with a higher DSST score. We conducted these analyses by using multiple logistic regression as performed by SUDAAN PROC RLOGIST, and we defined high serum total folate as a value above the 75th percentile (ie, radioassay: 55 nmol/L; HPLC: 66 nmol/L)

25. MORRIS, 2012

Full citation: Morris MS, Selhub J, Jacques PF. 2012. Vitamin B-12 and folate status in relation to decline in scores on the mini-mental state examination in the framingham heart study. J Am Geriatr Soc 60(8): 1457-1464.

Funding: Funded by U.S. Department of Agriculture Agreement 58–1950–7-707 and National Institutes of Health Grant 1 R01 NS062877–01A2.

FRAMINGHAM HEART STUDY AND COGNITIVE FUNCTION, 1986-1990 COHORT

Age: 74.8 (mean)	**Study design:** Prospective (**n** = 549)
Gender: Male and Female **Ethnicities:**	**Country:** United States **Region:** **State:** Massachusetts
Inclusion criteria:	**Exclusion critieria:** plasma vitamin B-12 concentrations above reference range (118-701 pmol/L)

25.1. Exposure: Folate Supplement use

Method	Description	Analysis
questionnaire	Food frequency questionnaire (FFQ)... The FFQ also contained items about supplement use (multivitamins, brand and frequency of use; single-vitamin supplements, dosages)	Participant responses for food items were converted to nutrient intakes using standard nutrient database information

Outcomes

	Outcome	Diagnostic Description
A	Annual Change in Mini-Mental State Examination (MMSE) Score (medical professional or test)	The MMSE is a brief, crude dementia-screening instrument consisting of 16 individual questions or simple tasks. Tasks involve naming objects, repeating and remembering a series of three common words, copying a figure, writing a sentence, repeating a phrase, spelling a word backward, and folding a piece of paper and placing it on a desk, table, or floor. Functions assessed include orientation (10 points), registration (3 points), attention and calculation (5 points), recall (3 points), and language and praxis (9 points)

Results

25.1.A Annual Change in Mini-Mental State Examination (MMSE) Score

Population: Framingham Heart Study and Cognitive Function
Exposure: Folate Supplement use
Outcome: Annual Change in Mini-Mental State Examination (MMSE) Score
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
High B12 (>=258 pmol/L), No folate supplementation	-	-0.16 (-0.21, -0.11)	
High B12 (>=258 pmol/L), Folate supplementation	-	-0.13 (-0.23, -0.03)	
Low B12 (<258 pmol/L), No folate supplementation	-	-0.33 (-0.39, -0.27)	
Low B12 (<258 pmol/L), Folate supplementation	-	-0.78 (-1.0, -0.56)	

Statistical Method(s)

Endpoints: Annual Change in Mini-Mental State Examination (MMSE) Score
Adjustment factors: age, baseline serum creatinine, body mass index (BMI), current smoking status, educational achievement, sex
Statistical metric: adjusted beta
Statistical metric description: Because hypotheses concerning cognitive harm from high folate status relate specifically to the effect of consuming folic acid, the synthetic form of folate, on people who are deficient in vitamin B-12, the effect of the interaction between time and the use of supplements containing folic acid at examination 20 (vs nonuse of such supplements) on cognitive decline was also considered in cohort members stratified according to vitamin B-12 status (dichotomous classification)

25.2. Exposure: Plasma folate stratified by vitamin B12 status

Method	Description	Analysis
Serum assay	Plasma concentrations of folate and vitamin B-12 were measured in nonfasting blood samples. Folate concentration was determined using a microbial (Lactobacillus casei) assay with a 96-well plate and manganese supplementation as described previously.Vitamin B-12 concentration was determined using a radioassay kit (Ciba-Corning, Medifield, MA) and measured as pmol/L.	Subjects divided by high/low plasma vitamin B12 (at 258 pmol/L) and into quintiles of plasma folate (<5, 5-7.89, 7.7-12, 12.01-21.7, and >=21.75 nmol/L)

Outcomes

	Outcome	Diagnostic Description
A	Annual Change in Mini-Mental State Examination (MMSE) Score (medical professional or test)	The MMSE is a brief, crude dementia-screening instrument consisting of 16 individual questions or simple tasks. Tasks involve naming objects, repeating and remembering a series of three common words, copying a figure, writing a sentence, repeating a phrase, spelling a word backward, and folding a piece of paper and placing it on a desk, table, or floor. Functions assessed include orientation (10 points), registration (3 points), attention and calculation (5 points), recall (3 points), and language and praxis (9 points)

Results

25.2.A Annual Change in Mini-Mental State Examination (MMSE) Score

Population: Framingham Heart Study and Cognitive Function, 1986-1990 cohort over 8 years of follow-up
Exposure: Plasma folate stratified by vitamin B12 status
Outcome: Annual Change in Mini-Mental State Examination (MMSE) Score
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
High B12 (>=258 pmol/L), Q1 folate (<5 nmol/L)	57	-0.18 (-0.3, -0.06)	
High B12 (>=258 pmol/L), Q2 folate (5-7.69 nmol/L)	53	-0.14 (-0.27, -0.01)	0.62
High B12 (>=258 pmol/L), Q3 folate (7.7-12 nmol/L)	75	-0.17 (-0.27, -0.06)	0.85
High B12 (>=258 pmol/L), Q4 folate (12.01-21.7 nmol/L)	79	-0.14 (-0.24, -0.03)	0.57
High B12 (>=258 pmol/L), Q5 folate (>=21.75 nmol/L)	93	-0.14 (-0.23, -0.05)	0.59
LowB12 (<258 pmol/L), Q1 folate (<5 nmol/L)	60	-0.32 (-0.44, -0.21)	
LowB12 (<258 pmol/L), Q2 folate (5-7.69 nmol/L)	64	-0.32 (-0.42, -0.21)	0.94
LowB12 (<258 pmol/L), Q3 folate (7.7-12 nmol/L)	44	-0.22 (-0.35, -0.08)	0.25
LowB12 (<258 pmol/L), Q4 folate (12.01-21.7 nmol/L)	39	-0.28 (-0.42, -0.14)	0.67
LowB12 (<258 pmol/L), Q5 folate (>=21.75 nmol/L)	24	-0.92 (-1.09, -0.74)	0.001

Statistical Method(s)

Endpoints: Annual Change in Mini-Mental State Examination (MMSE) Score
Adjustment factors: age, alcohol use vs nonuse, baseline BMI, educational achievement, sex
Statistical metric: adjusted beta
Statistical metric description: For plasma vitamin B-12 and plasma folate and other participant characteristics related to the MMSE score at P </=.2, exposure categories were created, and the least squares mean (95% CI) MMSE score was estimated for each category after controlling for the other characteristics also associated with MMSE score at P</= .2.

FRAMINGHAM HEART STUDY AND COGNITIVE FUNCTION, BASELINE 1986-1990

Age: 74.8 (mean)	**Study design:** Cross-sectional (**n =** 549)
Gender: Male and Female **Ethnicities:**	**Country:** United States **Region:** **State:** Massachusetts
Inclusion criteria:	**Exclusion critieria:** plasma vitamin B-12 concentrations above reference range (118-701 pmol/L)

25.3. Exposure: Plasma folate

Method	Description	Analysis
assay	Plasma concentrations of folate and vitamin B-12 were measured in nonfasting blood samples. Folate concentration was determined using a microbial (Lactobacillus casei) assay with a 96-well plate and manganese supplementation as described previously	Subjects divided by quintiles (n109-110 each) 1st quintile: 0.54–4.8 nmol/L; 2nd quintile: 4.9–7.5 nmol/L; 3rd quintile: 7.52–11.49 nmol/L; 4th quintile: 11.5–20.14 nmol/L; 5th quintile: 20.2–149 nmol/L

Outcomes

	Outcome	Diagnostic Description
A	Mini-Mental State Examination (MMSE) (medical professional or test)	The MMSE is a brief, crude dementia-screening instrument consisting of 16 individual questions or simple tasks. Tasks involve naming objects, repeating and remembering a series of three common words, copying a figure, writing a sentence, repeating a phrase, spelling a word backward, and folding a piece of paper and placing it on a desk, table, or floor. Functions assessed include orientation (10 points), registration (3 points), attention and calculation (5 points), recall (3 points), and language and praxis (9 points)

Results

25.3.A Mini-Mental State Examination (MMSE)

Population: Framingham Heart Study and Cognitive Function
Exposure: Plasma folate
Outcome: Mini-Mental State Examination (MMSE)
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
1st quintile (0.54–4.8 nmol/L)	110	-	
2nd quintile (4.9–7.5 nmol/L)	109	-	
3rd quintile (7.52–11.49 nmol/L)	110	-	
4th quintile (11.5–20.14 nmol/L)	110	-	
5th quintile (20.2–149 nmol/L)	110	-	0.69

Statistical Method(s)

Endpoints: Mini-Mental State Examination (MMSE)
Adjustment factors:
Statistical metric: mean
Statistical metric description: For plasma vitamin B-12 and plasma folate and other participant characteristics related to the MMSE score at P </=.2, exposure categories were created, and the least squares mean (95% CI) MMSE score was estimated for each category after controlling for the other characteristics also associated with MMSE score at P</= .2.

25.4. Exposure: Plasma vitamin B12

Method	Description	Analysis
assay	Plasma concentrations ... vitamin B-12 were measured in nonfasting blood samples. Vitamin B-12 concentration was determined using a radioassay kit.	Subjects divided by quintiles (n109-110 each) 1st quintile: 18.6-186 pmol/L; 2nd quintile: 187-256.8 pmol/L; 3rd quintile: 257-342.8 pmol/L; 4th quintile: 342.9-435 pmol/L; 5th quintile: 435.4-695 pmol/L

Outcomes

	Outcome	Diagnostic Description
A	Mini-Mental State Examination (MMSE) (medical professional or test)	The MMSE is a brief, crude dementia-screening instrument consisting of 16 individual questions or simple tasks. Tasks involve naming objects, repeating and remembering a series of three common words, copying a figure, writing a sentence, repeating a phrase, spelling a word backward, and folding a piece of paper and placing it on a desk, table, or floor. Functions assessed include orientation (10 points), registration (3 points), attention and calculation (5 points), recall (3 points), and language and praxis (9 points)

Results

25.4.A Mini-Mental State Examination (MMSE)

Population: Framingham Heart Study and Cognitive Function, baseline 1986-1990
Exposure: Plasma vitamin B12
Outcome: Mini-Mental State Examination (MMSE)
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
1st quintile (18.6-186 pmol/L)	109	-	
2nd quintile (187-256.8 pmol/L)	110	-	
3rd quintile (257-342.8 pmol/L)	110	-	
4th quintile (342.9-435 pmol/L)	110	-	
5th quintile (435.4-695 pmol/L)	110	-	

Statistical Method(s)

Endpoints: Mini-Mental State Examination (MMSE)
Adjustment factors:
Statistical metric: mean
Statistical metric description: For plasma vitamin B-12 and plasma folate and other participant characteristics related to the MMSE score at P</=.2, exposure categories were created, and the least squares mean (95% CI) MMSE score was estimated for each category after controlling for the other characteristics also associated with MMSE score at P</= .2.

26. NILSSON, 2001

Full citation: Nilsson K, Gustafson L, Hultberg B. 2001. Improvement of cognitive functions after cobalamin/folate supplementation in elderly patients with dementia and elevated plasma homocysteine. Int J Geriatr Psychiatry 16(6): 609-614.

Funding: The present study was supported by grants from the Swedish Medical Research Council (grant no. 003950), the Swedish Heart-Lung Foundation, the Albert Pahlsson Foundation, the Alzheimer Foundation, Sweden, and the County Council of Skane.

SWEDISH ELDERLY VITAMIN INTERVENTION

Age: 78.4 (mean)	**Study design:** Controlled trial (**n =** 33)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Sweden **Region:** **State:**
Inclusion criteria: living in own homes, symptoms of organic brain disease	**Exclusion critieria:** acute or unstable physical conditions, non-organic psychiatric diseases, severely demented and could not cooperate in the tests before or after treatment, vitamin supplementation

26.1. Exposure: Folic acid (5mg/day) and B12 (1mg/day) for 2 months

Method	Description	Analysis
intervention	mg/day; 2 months of oral supplementation with cyanocobalamin (1 mg/day) and folic acid (5 mg/day); lab assays also performed	intervention

Outcomes

	Outcome	Diagnostic Description
A	Mini-Mental State Examination (MMSE) (medical professional or test)	The patients were assessed with the MMSE...before and after 2 months of vitamin substitution. MMSE scores vary from 0 to 30, with lower scores signifying severe cognitive impairment.
B	Short cognitive test (SKT) (medical professional or test)	The patients were assessed ... with 'a short cognitive performance test for assessing memory and attention' (SKT) ... before and after 2 months of vitamin substitution. The SKT consists of nine sub-tests, each limited to a maximum time of 60s, and serves the purpose of assessing the severity of impairments of memory and attention in the sense of information processing speed. The SKT total score may vary from 0 to 27, with higher scores signifying severe cognitive impairment.

Results

26.1.A Mini-Mental State Examination (MMSE)

Population: Swedish elderly B-vitamin intervention
Exposure: Folic acid (5mg/day) and B12 (1mg/day) for 2 months
Outcome: Mini-Mental State Examination (MMSE)
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
P-homocysteine <19.9 umol/L	11	-	
P-homocysteine >19.9 umol/L	17	-	0.01

26.1.B Short cognitive test (SKT)

Population: Swedish elderly B-vitamin intervention
Exposure: Folic acid (5mg/day) and B12 (1mg/day) for 2 months
Outcome: Short cognitive test (SKT)
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
P-homocysteine <19.9 umol/L	11	-	
P-homocysteine >19.9 umol/L	17	-	0.01

Statistical Method(s)

Endpoints: Mini-Mental State Examination (MMSE); Short cognitive test (SKT)
Adjustment factors:
Statistical metric: mean
Statistical metric description: Changes within group analyzed using Wilcoxon's matched-pairs signed rank test, and between-group differences were analyzed using Mann-Whitney U-test.

27. SELHUB, 2009

Full citation: Selhub J, Morris MS, Jacques PF, Rosenberg IH. 2009. Folate-vitamin B-12 interaction in relation to cognitive impairment, anemia, and biochemical indicators of vitamin B-12 deficiency. Am J Clin Nutr 89(2): 702S-706S.

Funding: Supported by the USDA (agreements 1950-51520-008-00D and 58-1950-9-001 and grant 2006-35200-17198) and by the NIH (R03 AG021536-01).

SENIORS, NHANES (1999-2002)

Age: >/= 60 years	**Study design:** Cross-sectional (**n =** 1302)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** United States **Region:** **State:**
Inclusion criteria: More than 60 years	**Exclusion critieria:**

27.1. Exposure: Serum folate and B12 Concomitant status

Method	Description	Analysis
assay	blood samples were drawn and analyzed for biochemical markers, and a complete blood count was performed.	We defined low vitamin B-12 status as serum vitamin B-12 <148 pmol/L or serum MMA > 210 nmol/L [ie, above the published reference range for serum vitamin B-12–replete survey participants with normal serum creatinine concentrations... we used distribution-based cutoffs to define high serum folate (i.e. > 59 nmol/L, 80th percentile)

Outcomes

	Outcome	Diagnostic Description
A	Cognitive Impairment (medical professional or test)	cognitive impairment (ie, Digit Symbol-Substitution subtest score <34/133, the 20th percentile)

Results

27.1.A Cognitive Impairment

Population: Seniors, NHANES (1999-2002)
Exposure: Serum folate and B12 Concomitant status
Outcome: Cognitive Impairment
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Normal B12 (>=148), Normal Folate (<=59)	826	1.0	
Normal B12 (>=148), High Folate (>59)	180	0.4 (0.2, 0.9)	
Low B12 (<148), Normal Folate (<=59)	253	1.7 (1.01, 2.9)	0.05
Low B12 (<148), High Folate (>59)	42	5.1 (2.7, 9.5)	0.05

Statistical Method(s)

Endpoints: Cognitive Impairment
Adjustment factors: homocysteine concentrations
Statistical metric: adjusted odds ratio
Statistical metric description: No methods description, only description of model adjustment factors "the odds ratios were only modestly affected by controlling for homocysteine concentrations"

28. TETTAMANTI, 2006

Full citation: Tettamanti M, Garri MT, Nobili A, Riva E, Lucca U. 2006. Low folate and the risk of cognitive and functional deficits in the very old: the Monzino 80-plus study. J Am Coll Nutr 25(6): 502-508.

Funding: This study is being supported by a research grant from the Fondazione Italo Monzino, Milano, Italy.

MONZINO 80-PLUS STUDY

Age: 87.4 (mean)	**Study design:** Cross-sectional (**n =** 471)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Italy **Region:** Olona Valley, Northern Italy **State:**
Inclusion criteria: >80 years	**Exclusion critieria:** serum concentrations of vitamin B12 above 1000 pg/mL or folate above 15 ng/mL, vitamin B supplementation

28.1. Exposure: Serum folate

Method	Description	Analysis
assay	Fasting serum vitamin B12 and folate concentrations were determined by Microparticle Enzyme Immuno-Assay (Abbott IMx system).	Within-run coefficients of variation of these assays were between 4.3% and 4.5% for vitamin B12 and between 2.6% and 7.3% for folate. Samples that fell above and below the reference range were reassayed

Outcomes

	Outcome	Diagnostic Description
A	Dementia (medical professional or test)	The diagnosis of dementia was made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition

Results

28.1.A Dementia

Population: Monzino 80-plus study
Exposure: Serum folate
Outcome: Dementia
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
>6.1 ng/mL	95	1.0	
4.0–6.1 ng/mL	153	5.4 (2.53, 12.73)	0.05
<4.0 ng/mL	189	6.56 (3.11, 15.29)	0.05

Statistical Method(s)

Endpoints: Dementia
Adjustment factors: age, diabetes, educational achievement, hypertension, myocardial infarction, plasma creatinine, previous smoking habit, sex, stroke, vitamin B12 status
Statistical metric: adjusted odds ratio
Statistical metric description: Univariate and multivariate logistic regression analyses were applied to estimate the crude and adjusted odds ratios (ORs) of being in the dementia group in the three tertile concentrations of vitamin B12 and folate: these tertiles were obtained using the distribution of concentrations of these biochemical variables in dementia-free participants with a MMSE score >23

28.2. Exposure: Serum vitamin B12

Method	Description	Analysis
assay	Fasting serum vitamin B12 ...concentrations were determined by Microparticle Enzyme Immuno-Assay (Abbott IMx system)	Within-run coefficients of variation of these assays were between 4.3% and 4.5% for vitamin B12 and between 2.6% and 7.3% for folate. Samples that fell above and below the reference range were reassayed

Outcomes

	Outcome	Diagnostic Description
A	Dementia (medical professional or test)	The diagnosis of dementia was made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition

Results

28.2.A Dementia

Population: Monzino 80-plus study
Exposure: Serum vitamin B12
Outcome: Dementia
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
>350 pg/mL	158	1.0	
246–350 pg/mL	136	0.93 (0.54, 1.59)	
<246 pg/mL	143	1.09 (0.65, 1.84)	

Statistical Method(s)

Endpoints: Dementia
Adjustment factors: age, diabetes, educational achievement, folate concentration, hypertension, myocardial infarction, plasma creatinine, previous smoking habit, sex, stroke
Statistical metric: adjusted odds ratio
Statistical metric description: Univariate and multivariate logistic regression analyses were applied to estimate the crude and adjusted odds ratios (ORs) of being in the dementia group in the three tertile

concentrations of vitamin B12 and folate: these tertiles were obtained using the distribution of concentrations of these biochemical variables in dementia-free participants with a MMSE score >23

29. TUCKER, 2005

Full citation: Tucker KL, Qiao N, Scott T, Rosenberg I, Spiro A, 3rd. 2005. High homocysteine and low B vitamins predict cognitive decline in aging men: the Veterans Affairs Normative Aging Study. Am J Clin Nutr 82(3): 627-635.

Funding: Supported in part by the USDA Agricultural Research Service, under agreement number 58-1950-9-001 and by NIA grant no. AG21790-01. The Cognition and Health in Aging Men Project (CHAMP) is supported by the Research Services of the US Department of Veterans Affairs, the National Institutes of Health (grants R01-AA08941, 01-AG13006, R01-AG14345, R01-AG18436, 5-P42-ES05947, and R01-ES05257), and the US Department of Agriculture, Agricultural Research Service (contract 53-K06-510). The VA Normative Aging Study is supported by the Cooperative Studies Program/Epidemiology Research and Information Center of the US Department of Veterans Affairs, and is a component of the Massachusetts Veterans Epidemiology Research and Information Center.

VETERANS AFFAIRS NORMATIVE AGING STUDY (NAS)

Age: 54-81 yrs	**Study design:** Prospective (**n =** 321)
Gender: Male **Ethnicities:**	**Country:** United States **Region:** Boston **State:** Massachusetts
Inclusion criteria: free of heart disease or other major health problems	**Exclusion critieria:**

29.1. Exposure: Folate, dietary intake

Method	Description	Analysis
questionnaire	Willett semiquantitative food-frequency questionnairerecord the number of times they consume each of 126 food items per month, week, or day. Vitamin and mineral supplement use was also asked on this questionnaire and was included in the total nutrient intake estimates	Questionnaires with improbable intakes (>16.75 or <2.51 MJ) were excluded from further analysis

Outcomes

	Outcome	Diagnostic Description
A	Change in figure copying score by tertile category (medical professional or test)	In the spatial copying task, participants are asked to copy a circle, crossed rectangles, a vertical diamond, and a cube (from the CERAD battery) as well as tilted triangles, an 8-dot circle, a horizontal diamond, and a tapered box (from the Developmental Test of Visual-Motor Integration;VMI)(25, 27). The accuracy of the copied figures is scored by trained staff using criteria from the CERAD and VMI. The resulting score is the total number of figures drawn correctly; the maximum score is 9. A second score is weighted by the degree of difficulty of the figure, resulting in a maximum score of 26.

	Outcome	Diagnostic Description
B	Constructional praxis: spatial copying, sum of drawings (medical professional or test)	In the spatial copying task, participants are asked to copy a circle, crossed rectangles, a vertical diamond, and a cube (from the CERAD battery) as well as tilted triangles, an 8-dot circle, a horizontal diamond, and a tapered box (from the Developmental Test of Visual-Motor Integration; VMI) (25, 27). The accuracy of the copied figures is scored by trained staff using criteria from the CERAD and VMI. The resulting score is the total number of figures drawn correctly; the maximum score is 9. A second score is weighted by the degree of difficulty of the figure, resulting in a maximum score of 26.
C	Constructional praxis: spatial copying, sum of drawings: Including Baseline measures (medical professional or test)	In the spatial copying task, participants are asked to copy a circle, crossed rectangles, a vertical diamond, and a cube (from the CERAD battery) as well as tilted triangles, an 8-dot circle, a horizontal diamond, and a tapered box (from the Developmental Test of Visual-Motor Integration; VMI) (25, 27). The accuracy of the copied figures is scored by trained staff using criteria from the CERAD and VMI. The resulting score is the total number of figures drawn correctly; the maximum score is 9. A second score is weighted by the degree of difficulty of the figure, resulting in a maximum score of 26.
D	Language: Verbal fluency (medical professional or test)	Language: Verbal Fluency, number correct. The verbal fluency test is also from the CERAD.Participants are asked to name as many animals as they can within 1 min
E	Language: Verbal fluency: Including baseline plasma and dietary measures (medical professional or test)	Language: Verbal Fluency, number correct. The verbal fluency test is also from the CERAD.Participants are asked to name as many animals as they can within 1 min
F	Mini-Mental State Examination (MMSE) (medical professional or test)	We also examined changes in Mini-Mental State Examination (MMSE) scores as a global measure of cognitive function
G	Recall Memory (medical professional or test)	The word list memory test is adapted from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (26). Ten words are presented on a computer screen consecutively, for 2 s each, and participants are then asked to recall these words. Three consecutive trials are administered, and the score is the sum of words remembered; the maximum score is 30.
H	Recall Memory: Including baseline plasma and dietary measures (medical professional or test)	The word list memory test is adapted from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (26). Ten words are presented on a computer screen consecutively, for 2 s each, and participants are then asked to recall these words. Three consecutive trials are administered, and the score is the sum of words remembered; the maximum score is 30.
I	Working Memory (medical professional or test)	The Backward Digit Span test is from the Revised Wechsler Adult Intelligence Scale (25). Participants are read a list of digits and asked to recall these in backward sequence. The score is the longest span of digits recalled correctly in backward order, with a maximum of 8.

Results

29.1.A Change in figure copying score by tertile category

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, dietary intake

Outcome: Change in figure copying score by tertile category
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Folate, diet	-	-	

29.1.B Constructional praxis: spatial copying, sum of drawings

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, dietary intake
Outcome: Constructional praxis: spatial copying, sum of drawings
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, diet	287	0.67	0.01

29.1.C Constructional praxis: spatial copying, sum of drawings: Including Baseline measures

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, dietary intake
Outcome: Constructional praxis: spatial copying, sum of drawings: Including Baseline measures
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, diet	-	0.71	0.05

29.1.D Language: Verbal fluency

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, dietary intake
Outcome: Language: Verbal fluency
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, diet	245	1.44	0.05

29.1.E Language: Verbal fluency: Including baseline plasma and dietary measures

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, dietary intake
Outcome: Language: Verbal fluency: Including baseline plasma and dietary measures
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, diet	-	1.35	

29.1.F Mini-Mental State Examination (MMSE)

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, dietary intake
Outcome: Mini-Mental State Examination (MMSE)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, diet	278	0.08	

29.1.G Recall Memory

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, dietary intake
Outcome: Recall Memory
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, diet	241	0.31	

29.1.H Recall Memory: Including baseline plasma and dietary measures

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, dietary intake
Outcome: Recall Memory: Including baseline plasma and dietary measures
Statistical metric: adjusted coefficient

Group	N	adjusted coefficient 95% CI (low, high)	*p*-value
Folate, diet	-	0.28	

29.1.I Working Memory

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, dietary intake
Outcome: Working Memory
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, diet	242	0.11	

Statistical Method(s)

Endpoints: Language: Verbal fluency: Including baseline plasma and dietary measures; Constructional praxis: spatial copying, sum of drawings: Including Baseline measures
Adjustment factors: age, alcohol intake, baseline cognitive measures, baseline plasma or dietary measures, body mass index (BMI), diabetes, educational achievement, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification, total energy intake
Statistical metric: adjusted beta
Statistical metric description: We also regressed the follow-up cognitive scores on initial dietary intake measures for folate, vitamin B-6, and B-12 by using the same set of covariates described for the plasma analyses, except that serum creatinine was replaced with total energy intake. Dietary measures were also skewed and, therefore, were log transformed before inclusion in the regression models. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS

Endpoints: Mini-Mental State Examination (MMSE); Recall Memory
Adjustment factors: age, alcohol intake, baseline cognitive measures, body mass index (BMI), diabetes, educational achievement, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification, total energy intake
Statistical metric: adjusted beta
Statistical metric description: We also regressed the follow-up cognitive scores on initial dietary intake measures for folate, vitamin B-6, and B-12 by using the same set of covariates described for the plasma analyses, except that serum creatinine was replaced with total energy intake. Dietary measures were also skewed and, therefore, were log transformed before inclusion in the regression models. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS.

Endpoints: Change in figure copying score by tertile category
Adjustment factors:
Statistical metric: t-test
Statistical metric description: All baseline dietary and plasma nutrient measures were assessed before fortification of the food supply with folic acid. In a final set of linear models, all measures of either plasma B vitamins and homocysteine or of dietary B vitamin intake were included jointly in the fully adjusted models to determine whether one or more of these contributed independently to the result. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS.

Endpoints: Working Memory
Adjustment factors: age, alcohol intake, baseline cognitive measures, body mass index (BMI), diabetes, educational achievement, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification, total energy intake
Statistical metric: adjusted beta
Statistical metric description: We also regressed the follow-up cognitive scores on initial dietary intake measures for folate, vitamin B-6, and B-12 by using the same set of covariates described for the plasma analyses, except that serum creatinine was replaced with total energy intake. Dietary measures were also skewed and, therefore, were log transformed before inclusion in the regression models.

Endpoints: Recall Memory: Including baseline plasma and dietary measures
Adjustment factors: age, alcohol intake, baseline cognitive measures, baseline plasma or dietary measures, body mass index (BMI), diabetes, educational achievement, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification, total energy intake
Statistical metric: adjusted coefficient
Statistical metric description: We also regressed the follow-up cognitive scores on initial dietary intake measures for folate, vitamin B-6, and B-12 by using the same set of covariates described for the plasma analyses, except that serum creatinine was replaced with total energy intake. Dietary measures were also skewed and, therefore, were log transformed before inclusion in the regression models. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS.

Endpoints: Constructional praxis: spatial copying, sum of drawings; Language: Verbal fluency
Adjustment factors: age, alcohol intake, baseline cognitive measures, body mass index (BMI), diabetes, educational achievement, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification, total energy intake
Statistical metric: adjusted beta
Statistical metric description: We also regressed the follow-up cognitive scores on initial dietary intake measures for folate, vitamin B-6, and B-12 by using the same set of covariates described for the plasma analyses, except that serum creatinine was replaced with total energy intake. Dietary measures were also skewed and, therefore, were log transformed before inclusion in the regression models. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS

29.2. Exposure: Folate, plasma

Method	Description	Analysis
plasma assay	Plasma folate ... measured by radioassay with the use of a commercially available kit from Bio-Rad (Hercules, CA).	The CVs for these assays in our laboratory are ...4.3% for folate

Outcomes

	Outcome	Diagnostic Description
A	Change in figure copying score by tertile category (medical professional or test)	In the spatial copying task, participants are asked to copy a circle, crossed rectangles, a vertical diamond, and a cube (from the CERAD battery) as well as tilted triangles, an 8-dot circle, a horizontal diamond, and a tapered box (from the Developmental Test of Visual-Motor Integration;VMI)(25, 27). The accuracy of the copied figures is scored by trained staff using criteria from the CERAD and VMI. The resulting score is the total number of figures drawn correctly; the maximum score is 9. A second score is weighted by the degree of difficulty of the figure, resulting in a maximum score of 26.
B	Constructional praxis: spatial copying, sum of drawings (medical professional or test)	In the spatial copying task, participants are asked to copy a circle, crossed rectangles, a vertical diamond, and a cube (from the CERAD battery) as well as tilted triangles, an 8-dot circle, a horizontal diamond, and a tapered box (from the Developmental Test of Visual-Motor Integration; VMI) (25, 27). The accuracy of the copied figures is scored by trained staff using criteria from the CERAD and VMI. The resulting score is the total number of figures drawn correctly; the maximum score is 9. A second score is weighted by the degree of difficulty of the figure, resulting in a maximum score of 26.
C	Constructional praxis: spatial copying, sum of drawings: including baseline plasma and dietary measures (medical professional or test)	In the spatial copying task, participants are asked to copy a circle, crossed rectangles, a vertical diamond, and a cube (from the CERAD battery) as well as tilted triangles, an 8-dot circle, a horizontal diamond, and a tapered box (from the Developmental Test of Visual-Motor Integration; VMI) (25, 27). The accuracy of the copied figures is scored by trained staff using criteria from the CERAD and VMI. The resulting score is the total number of figures drawn correctly; the maximum score is 9. A second score is weighted by the degree of

	Outcome	Diagnostic Description
		difficulty of the figure, resulting in a maximum score of 26.
D	Language: Verbal fluency (medical professional or test)	Language: Verbal Fluency, number correct. The verbal fluency test is also from the CERAD.Participants are asked to name as many animals as they can within 1 min
E	Language: verbal fluency: including baseline plasma and dietary measures (medical professional or test)	Language: Verbal Fluency, number correct. The verbal fluency test is also from the CERAD. Participants are asked to name as many animals as they can within 1 min
F	Mini-Mental State Examination (MMSE) (medical professional or test)	examined changes in Mini-Mental State Examination (MMSE) scores as a global measure of cognitive function (24)
G	Recall Memory (medical professional or test)	Recall memory; word lists, total of 3 trials. The word list memory test is adapted from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (26). Ten words are presented on a computer screen consecutively, for 2 s each, and participants are then asked to recall these words. Three consecutive trials are administered, and the score is the sum of words remembered; the maximum score is 30.
H	Recall Memory: including baseline plasma and dietary measures (medical professional or test)	Recall memory; word lists, total of 3 trials. The word list memory test is adapted from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (26). Ten words are presented on a computer screen consecutively, for 2 s each, and participants are then asked to recall these words. Three consecutive trials are administered, and the score is the sum of words remembered; the maximum score is 30.
I	Working Memory (medical professional or test)	Working memory: backward digit span, longest span recalled; The Backward Digit Span test is from the Revised Wechsler Adult Intelligence Scale (25). Participants are read a list of digits and asked to recall these in backward sequence. The score is the longest span of digits recalled correctly in backward order, with a maximum of 8.

Results

29.2.A Change in figure copying score by tertile category

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, plasma
Outcome: Change in figure copying score by tertile category
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Folate, plasma	-	-	

29.2.B Constructional praxis: spatial copying, sum of drawings

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, plasma
Outcome: Constructional praxis: spatial copying, sum of drawings
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, plasma	-	1.0	0.0001

29.2.C Constructional praxis: spatial copying, sum of drawings: including baseline plasma and dietary measures

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, plasma
Outcome: Constructional praxis: spatial copying, sum of drawings: including baseline plasma and dietary measures
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, plasma	-	0.71	0.01

29.2.D Language: Verbal fluency

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, plasma
Outcome: Language: Verbal fluency
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, plasma	-	0.76	

29.2.E Language: verbal fluency: including baseline plasma and dietary measures

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, plasma
Outcome: Language: verbal fluency: including baseline plasma and dietary measures
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, plasma	-	0.69	

29.2.F Mini-Mental State Examination (MMSE)

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, plasma
Outcome: Mini-Mental State Examination (MMSE)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, plasma	-	0.12	

29.2.G Recall Memory

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, plasma
Outcome: Recall Memory
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, plasma	-	0.43	

29.2.H Recall Memory: including baseline plasma and dietary measures

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, plasma
Outcome: Recall Memory: including baseline plasma and dietary measures
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, plasma	-	-0.07	

29.2.I Working Memory

Population: Veterans Affairs Normative Aging Study
Exposure: Folate, plasma
Outcome: Working Memory
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Folate, plasma	-	-0.28	

Statistical Method(s)

Endpoints: Recall Memory; Mini-Mental State Examination (MMSE); Working Memory; Constructional praxis: spatial copying, sum of drawings
Adjustment factors: age, alcohol intake, baseline cognitive measures, body mass index (BMI), diabetes, educational achievement, serum creatinine, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification
Statistical metric: adjusted beta
Statistical metric description: All baseline dietary and plasma nutrient measures were assessed before fortification of the food supply with folic acid. In a final set of linear models, all measures of either plasma B vitamins and homocysteine or of dietary B vitamin intake were included jointly in the fully adjusted models to determine whether one or more of these contributed independently to the result. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS

Endpoints: Language: Verbal fluency
Adjustment factors: age, alcohol intake, baseline cognitive measures, body mass index (BMI), diabetes, educational achievement, serum creatinine, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification
Statistical metric: adjusted beta
Statistical metric description: All baseline dietary and plasma nutrient measures were assessed before fortification of the food supply with folic acid. In a final set of linear models, all measures of either plasma B vitamins and homocysteine or of dietary B vitamin intake were included jointly in the fully adjusted models to determine whether one or more of these contributed independently to the result. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS

Endpoints: Change in figure copying score by tertile category
Adjustment factors:
Statistical metric: t-test
Statistical metric description: All baseline dietary and plasma nutrient measures were assessed before fortification of the food supply with folic acid. In a final set of linear models, all measures of either plasma B vitamins and homocysteine or of dietary B vitamin intake were included jointly in the fully adjusted models to determine whether one or more of these contributed independently to the result. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS.

Endpoints: Recall Memory: including baseline plasma and dietary measures; Language: verbal fluency: including baseline plasma and dietary measures; Constructional praxis: spatial copying, sum of drawings: including baseline plasma and dietary measures
Adjustment factors: age, alcohol intake, baseline cognitive measures, baseline plasma or dietary measures, body mass index (BMI), diabetes, educational achievement, serum creatinine, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification
Statistical metric: adjusted beta
Statistical metric description: All baseline dietary and plasma nutrient measures were assessed before fortification of the food supply with folic acid. In a final set of linear models, all measures of either plasma B vitamins and homocysteine or of dietary B vitamin intake were included jointly in the fully adjusted models to determine whether one or more of these contributed independently to the result. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS.

29.3. Exposure: Vitamin B12, dietary intake

Method	Description	Analysis
questionnaire	Willett semiquantitative food-frequency questionnairerecord the number of times they consume each of 126 food items per month, week, or day. Vitamin and mineral supplement use was also asked on this questionnaire and was included in the total nutrient intake estimates	Questionnaires with improbable intakes (>16.75 or <2.51 MJ) were excluded from further analysis

Outcomes

	Outcome	Diagnostic Description
A	Constructional praxis: spatial copying, sum of drawings (medical professional or test)	In the spatial copying task, participants are asked to copy a circle, crossed rectangles, a vertical diamond, and a cube (from the CERAD battery) as well as tilted triangles, an 8-dot circle, a horizontal diamond, and a tapered box (from the Developmental Test of Visual-Motor Integration; VMI) (25, 27). The accuracy of the copied figures is scored by trained staff using criteria from the CERAD and VMI. The

	Outcome	Diagnostic Description
		resulting score is the total number of figures drawn correctly; the maximum score is 9. A second score is weighted by the degree of difficulty of the figure, resulting in a maximum score of 26.
B	Constructional praxis: spatial copying, sum of drawings: Including Baseline measures (medical professional or test)	In the spatial copying task, participants are asked to copy a circle, crossed rectangles, a vertical diamond, and a cube (from the CERAD battery) as well as tilted triangles, an 8-dot circle, a horizontal diamond, and a tapered box (from the Developmental Test of Visual-Motor Integration; VMI) (25, 27). The accuracy of the copied figures is scored by trained staff using criteria from the CERAD and VMI. The resulting score is the total number of figures drawn correctly; the maximum score is 9. A second score is weighted by the degree of difficulty of the figure, resulting in a maximum score of 26.
C	Language: Verbal fluency (medical professional or test)	Language: Verbal Fluency, number correct. The verbal fluency test is also from the CERAD.Participants are asked to name as many animals as they can within 1 min
D	Language: Verbal fluency: Including baseline plasma and dietary measures (medical professional or test)	Language: Verbal Fluency, number correct. The verbal fluency test is also from the CERAD.Participants are asked to name as many animals as they can within 1 min
E	Mini-Mental State Examination (MMSE) (medical professional or test)	We also examined changes in Mini-Mental State Examination (MMSE) scores as a global measure of cognitive function
F	Recall Memory (medical professional or test)	The word list memory test is adapted from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (26). Ten words are presented on a computer screen consecutively, for 2 s each, and participants are then asked to recall these words. Three consecutive trials are administered, and the score is the sum of words remembered; the maximum score is 30.
G	Recall Memory: Including baseline plasma and dietary measures (medical professional or test)	The word list memory test is adapted from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (26). Ten words are presented on a computer screen consecutively, for 2 s each, and participants are then asked to recall these words. Three consecutive trials are administered, and the score is the sum of words remembered; the maximum score is 30.
H	Working Memory (medical professional or test)	The Backward Digit Span test is from the Revised Wechsler Adult Intelligence Scale (25). Participants are read a list of digits and asked to recall these in backward sequence. The score is the longest span of digits recalled correctly in backward order, with a maximum of 8.

Results

29.3.A Constructional praxis: spatial copying, sum of drawings

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, dietary intake
Outcome: Constructional praxis: spatial copying, sum of drawings
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, diet	-	0.37	0.05

29.3.B Constructional praxis: spatial copying, sum of drawings: Including Baseline measures

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, dietary intake
Outcome: Constructional praxis: spatial copying, sum of drawings: Including Baseline measures
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, diet	-	0.07	

29.3.C Language: Verbal fluency

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, dietary intake
Outcome: Language: Verbal fluency
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, diet	245	0.38	

29.3.D Language: Verbal fluency: Including baseline plasma and dietary measures

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, dietary intake
Outcome: Language: Verbal fluency: Including baseline plasma and dietary measures
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, diet	-	-0.38	

29.3.E Mini-Mental State Examination (MMSE)

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, dietary intake
Outcome: Mini-Mental State Examination (MMSE)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, diet	278	0.14	

29.3.F Recall Memory

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, dietary intake
Outcome: Recall Memory
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, diet	241	-0.01	

29.3.G Recall Memory: Including baseline plasma and dietary measures

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, dietary intake

Outcome: Recall Memory: Including baseline plasma and dietary measures
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, diet	-	-0.22	

29.3.H Working Memory

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, dietary intake
Outcome: Working Memory
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, diet	242	0.12	

Statistical Method(s)

Endpoints: Language: Verbal fluency; Recall Memory; Constructional praxis: spatial copying, sum of drawings; Mini-Mental State Examination (MMSE)
Adjustment factors: age, alcohol intake, baseline cognitive measures, body mass index (BMI), diabetes, educational achievement, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification, total energy intake
Statistical metric: adjusted beta
Statistical metric description: We also regressed the follow-up cognitive scores on initial dietary intake measures for folate, vitamin B-6, and B-12 by using the same set of covariates described for the plasma analyses, except that serum creatinine was replaced with total energy intake. Dietary measures were also skewed and, therefore, were log transformed before inclusion in the regression models. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS.

Endpoints: Working Memory
Adjustment factors: age, alcohol intake, baseline cognitive measures, body mass index (BMI), diabetes, educational achievement, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification, total energy intake
Statistical metric: adjusted beta
Statistical metric description: We also regressed the follow-up cognitive scores on initial dietary intake measures for folate, vitamin B-6, and B-12 by using the same set of covariates described for the plasma analyses, except that serum creatinine was replaced with total energy intake. Dietary measures were also skewed and, therefore, were log transformed before inclusion in the regression models.

Endpoints: Language: Verbal fluency: Including baseline plasma and dietary measures; Constructional praxis: spatial copying, sum of drawings: Including Baseline measures; Recall Memory: Including baseline plasma and dietary measures
Adjustment factors: age, alcohol intake, baseline cognitive measures, baseline plasma or dietary measures, body mass index (BMI), diabetes, educational achievement, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification, total energy intake

Statistical metric: adjusted beta
Statistical metric description: We also regressed the follow-up cognitive scores on initial dietary intake measures for folate, vitamin B-6, and B-12 by using the same set of covariates described for the plasma analyses, except that serum creatinine was replaced with total energy intake. Dietary measures were also skewed and, therefore, were log transformed before inclusion in the regression models. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS

29.4. Exposure: Vitamin B12, plasma

Method	Description	Analysis
plasma assay	in pmol/L; Plasma vitamin B-12 concentrations measured by radioassay with the use of a commercially available kit from Bio-Rad (Hercules, CA).	The CVs for these assays in our laboratory are 4.7% for vitamin B-12

Outcomes

	Outcome	Diagnostic Description
A	Constructional praxis: spatial copying, sum of drawings (medical professional or test)	In the spatial copying task, participants are asked to copy a circle, crossed rectangles, a vertical diamond, and a cube (from the CERAD battery) as well as tilted triangles, an 8-dot circle, a horizontal diamond, and a tapered box (from the Developmental Test of Visual-Motor Integration; VMI) (25, 27). The accuracy of the copied figures is scored by trained staff using criteria from the CERAD and VMI. The resulting score is the total number of figures drawn correctly; the maximum score is 9. A second score is weighted by the degree of difficulty of the figure, resulting in a maximum score of 26.
B	Constructional praxis: spatial copying, sum of drawings: Including Baseline measures (medical professional or test)	In the spatial copying task, participants are asked to copy a circle, crossed rectangles, a vertical diamond, and a cube (from the CERAD battery) as well as tilted triangles, an 8-dot circle, a horizontal diamond, and a tapered box (from the Developmental Test of Visual-Motor Integration; VMI) (25, 27). The accuracy of the copied figures is scored by trained staff using criteria from the CERAD and VMI. The resulting score is the total number of figures drawn correctly; the maximum score is 9. A second score is weighted by the degree of difficulty of the figure, resulting in a maximum score of 26.
C	Language: Verbal fluency (medical professional or test)	Language: Verbal Fluency, number correct. The verbal fluency test is also from the CERAD.Participants are asked to name as many animals as they can within 1 min
D	Language: Verbal fluency: Including baseline plasma and dietary measures (medical professional or test)	Language: Verbal Fluency, number correct. The verbal fluency test is also from the CERAD.Participants are asked to name as many animals as they can within 1 min
E	Mini-Mental State Examination (MMSE) (medical professional or test)	examined changes in Mini-Mental State Examination (MMSE) scores as a global measure of cognitive function (24)
F	Recall Memory	Recall memory; word lists, total of 3 trials. The word list memory

	Outcome	Diagnostic Description
	(medical professional or test)	test is adapted from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (26). Ten words are presented on a computer screen consecutively, for 2 s each, and participants are then asked to recall these words. Three consecutive trials are administered, and the score is the sum of words remembered; the maximum score is 30.
G	Recall Memory: Including baseline plasma and dietary measures (medical professional or test)	Recall memory; word lists, total of 3 trials. The word list memory test is adapted from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (26). Ten words are presented on a computer screen consecutively, for 2 s each, and participants are then asked to recall these words. Three consecutive trials are administered, and the score is the sum of words remembered; the maximum score is 30.
H	Working Memory (medical professional or test)	Working memory: backward digit span, longest span recalled; The Backward Digit Span test is from the Revised Wechsler Adult Intelligence Scale (25). Participants are read a list of digits and asked to recall these in backward sequence. The score is the longest span of digits recalled correctly in backward order, with a maximum of 8.

Results

29.4.A Constructional praxis: spatial copying, sum of drawings

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, plasma
Outcome: Constructional praxis: spatial copying, sum of drawings
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, plasma	-	0.59	0.05

29.4.B Constructional praxis: spatial copying, sum of drawings: Including Baseline measures

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, plasma
Outcome: Constructional praxis: spatial copying, sum of drawings: Including Baseline measures
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, plasma	-	0.06	

29.4.C Language: Verbal fluency

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, plasma
Outcome: Language: Verbal fluency
Statistical metric: adjusted coefficient

Group	N	adjusted coefficient 95% CI (low, high)	*p*-value
B-12, plasma	-	0.06	

29.4.D Language: Verbal fluency: Including baseline plasma and dietary measures

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, plasma
Outcome: Language: Verbal fluency: Including baseline plasma and dietary measures
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, plasma	-	-0.51	

29.4.E Mini-Mental State Examination (MMSE)

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, plasma
Outcome: Mini-Mental State Examination (MMSE)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, plasma	-	-0.16	

29.4.F Recall Memory

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, plasma
Outcome: Recall Memory
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, plasma	-	-0.2	

29.4.G Recall Memory: Including baseline plasma and dietary measures

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, plasma
Outcome: Recall Memory: Including baseline plasma and dietary measures
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, plasma	-	-0.71	

29.4.H Working Memory

Population: Veterans Affairs Normative Aging Study
Exposure: Vitamin B12, plasma
Outcome: Working Memory
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
B-12, plasma	-	0.18	

Statistical Method(s)

Endpoints: Language: Verbal fluency
Adjustment factors: age, alcohol intake, baseline cognitive measures, body mass index (BMI), diabetes, educational achievement, serum creatinine, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification
Statistical metric: adjusted coefficient
Statistical metric description: All baseline dietary and plasma nutrient measures were assessed before fortification of the food supply with folic acid. In a final set of linear models, all measures of either plasma B vitamins and homocysteine or of dietary B vitamin intake were included jointly in the fully adjusted models to determine whether one or more of these contributed independently to the result. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS.

Endpoints: Language: Verbal fluency: Including baseline plasma and dietary measures
Adjustment factors: age, alcohol intake, baseline cognitive measures, baseline plasma or dietary measures, body mass index (BMI), diabetes, educational achievement, serum creatinine, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification
Statistical metric: adjusted beta
Statistical metric description: All baseline dietary and plasma nutrient measures were assessed before fortification of the food supply with folic acid. In a final set of linear models, all measures of either plasma B vitamins and homocysteine or of dietary B vitamin intake were included jointly in the fully adjusted models to determine whether one or more of these contributed independently to the result. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS.

Endpoints: Constructional praxis: spatial copying, sum of drawings: Including Baseline measures; Recall Memory: Including baseline plasma and dietary measures
Adjustment factors: age, alcohol intake, baseline cognitive measures, baseline plasma or dietary measures, body mass index (BMI), diabetes, educational achievement, serum creatinine, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification
Statistical metric: adjusted beta
Statistical metric description: All baseline dietary and plasma nutrient measures were assessed before fortification of the food supply with folic acid. In a final set of linear models, all measures of either plasma B vitamins and homocysteine or of dietary B vitamin intake were included jointly in the fully adjusted models to determine whether one or more of these contributed independently to the result. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS.

Endpoints: Working Memory
Adjustment factors: age, alcohol intake, baseline cognitive measures, body mass index (BMI), diabetes, educational achievement, serum creatinine, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification
Statistical metric: adjusted beta

Statistical metric description: All baseline dietary and plasma nutrient measures were assessed before fortification of the food supply with folic acid. In a final set of linear models, all measures of either plasma B vitamins and homocysteine or of dietary B vitamin intake were included jointly in the fully adjusted models to determine whether one or more of these contributed independently to the result. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS

Endpoints: Recall Memory; Mini-Mental State Examination (MMSE); Constructional praxis: spatial copying, sum of drawings
Adjustment factors: age, alcohol intake, baseline cognitive measures, body mass index (BMI), diabetes, educational achievement, serum creatinine, smoking, systolic blood pressure (SBP), time interval between 2 cognitive measures, time of second measure relative to folic acid fortification
Statistical metric: adjusted beta
Statistical metric description: All baseline dietary and plasma nutrient measures were assessed before fortification of the food supply with folic acid. In a final set of linear models, all measures of either plasma B vitamins and homocysteine or of dietary B vitamin intake were included jointly in the fully adjusted models to determine whether one or more of these contributed independently to the result. Test scores (backward digit span, word list recall, verbal fluency, figure copying, and MMSE) at follow-up were regressed, on baseline total homocysteine, plasma vitamin B-12, plasma folate, and PLP by using the regression procedure in SAS.

30. WAHLIN, 1996

Full citation: Wahlin A, Hill RD, Winblad B, Backman L. 1996. Effects of serum vitamin B12 and folate status on episodic memory performance in very old age: a population-based study. Psychol Aging 11(3): 487-496.

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KUNGSHOLMEN PROJECT, AGING AND DEMENTIA

Age: 84.8 (mean)	**Study design:** Cross-sectional (**n =** 250)
Gender: Male and Female **Ethnicities:**	**Country:** Sweden **Region:** Stockholm **State:**
Inclusion criteria: nondemented elderly	**Exclusion critieria:** drugs known to interact with folate uptake and lead to folate deficiency (i.e. anticonvulsants, antimetabolites, or trimethoprim), had been prescribed neuroleptics or antidepressants without having received a psychiatric diagnosis, psychiatric diagnosis (e.g., major depression, psychosis, or paranoia), vitamin B12 or folate supplementation

30.1. Exposure: Vitamin B12 and folate status

Method	Description	Analysis
Serum assay	vitamin B12 and folic acid, we used the radioimmunoassay method	For this reason, we set the cutoff for vitamin B12 at 200 pmol/L and the cutoff for folic acid at 11 nmol/L

Outcomes

	Outcome	Diagnostic Description
A	Recall (medical professional or test)	episodic memory tests described in this article, 48 concrete nouns were used... Participants were told to remember as many words as possible for subsequent free-recall tests. The words were bimodally presented; that is, they were shown on printed cards and simultaneously read aloud by the experimenter. The interitem interval was 1 s. Immediately after presentation of the last word in each list, an oral free-recall test was given. Two minutes were allowed for free recall of each list. After free recall of each list, yes-no recognition tests were given, in which the 12 target words were presented intermixed with an equal number of distractors collected from the same pool of items as the target words.
B	Recognition (medical professional or test)	yes-no recognition tests were given, in which the 12 target words were presented intermixed with an equal number of distractors

	Outcome	Diagnostic Description
		collected from the same pool of items as the target words. (Participants were not informed in advance about these tests.) In the recognition tests, the 24 words were presented consecutively in the same format as they had been presented during study, and participants responded orally. Each recognition test took about 2 min to complete

Results

30.1.A Recall

Population: Kungsholmen "Aging and Dementia" project
Exposure: Vitamin B12 and folate status
Outcome: Recall
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Vitamin B12 status	-	0.071	
Folic Acid status	-	0.105	
B12 x Folic Acid	-	0.171	

30.1.B Recognition

Population: Kungsholmen "Aging and Dementia" project
Exposure: Vitamin B12 and folate status
Outcome: Recognition
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Vitamin B12 status	-	0.006	
Folic Acid status	-	0.01	
B12 x Folic Acid	-	0.044	

Statistical Method(s)

Endpoints: Recall
Adjustment factors:
Statistical metric: adjusted beta
Statistical metric description: linear regression techniques applied, including age and interaction terms

Endpoints: Recognition
Adjustment factors:
Statistical metric: other
Statistical metric description: linear regression techniques applied, including age and interaction terms